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and the Southern Thoracic Surgical Association

14

25
Anniversary
Year

Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons
September 10–13, 1989, Baltimore Convention Center, Baltimore, MD (Page 149)

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association
November 9–11, 1989, Phoenician Golf and Tennis Resort, Scottsdale, AZ

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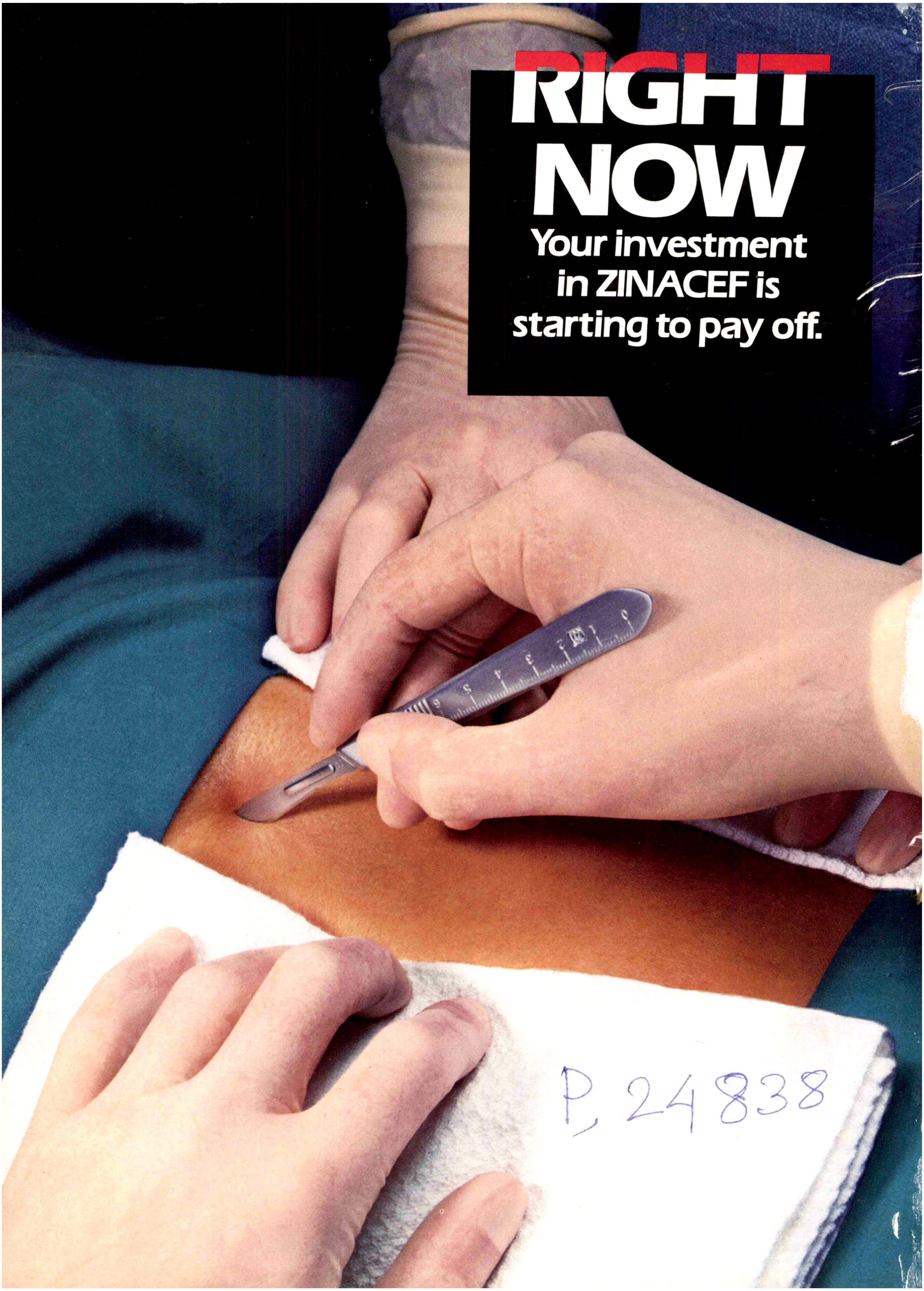
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P, 24838

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Your choice of ZINACEF for surgical prophylaxis is an investment that can yield outstanding returns in lower postop infection rates, shortened hospital stays, and an improved bottom line for your patients.

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A recent nationwide analysis revealed that each postoperative wound infection represents a nonreimbursable loss to a hospital of $2,467, on average.[2] By reducing the rate of infection, ZINACEF can help reduce these losses.

1. Slama TG, Sklar SJ, Misinski J, et al: Randomized comparison of cefamandole, cefazolin, and cefuroxime prophylaxis in open-heart surgery. *Antimicrob Agents Chemother* 1986;29:744-747.
2. Haley RW, White JW, Culver DH, et al: The financial incentive for hospitals to prevent nosocomial infections under the prospective payment system. *JAMA* 1987;257:1611-1614.

Please consult Brief Summary of Prescribing Information on next page before prescribing or administering ZINACEF.

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ZIN 346

ZINACEF® IM/IV **GLAXO**
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Brief summary. Before prescribing, consult complete Prescribing Information.

INDICATIONS AND USAGE: ZINACEF® is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *S pneumoniae* (formerly *D pneumoniae*), *H influenzae* (including ampicillin-resistant strains), *Klebsiella* sp, *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, and *E coli*.
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* sp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* sp, and *Enterobacter* sp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae* (including ampicillin-resistant strains), and *Klebsiella* sp.
5. **Meningitis** caused by *S pneumoniae*, *H influenzae* (including ampicillin-resistant strains), *N meningitidis*, and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *N gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *S aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. ZINACEF has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to ZINACEF.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, ZINACEF may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of ZINACEF may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (eg, vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. ZINACEF® (sterile cefuroxime sodium, Glaxo) should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of ZINACEF has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that ZINACEF therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: ZINACEF® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *C difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although ZINACEF® rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of ZINACEF should be reduced in patients with transient or persistent renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of ZINACEF may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Interference with Laboratory Tests: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving ZINACEF.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since ZINACEF is excreted in human milk, caution should be exercised when ZINACEF is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: ZINACEF® is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with ZINACEF and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence was seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

HOW SUPPLIED ZINACEF® is a dry, white to off-white powder supplied in vials and infusion packs.

Each vial contains cefuroxime sodium equivalent to 750 mg, 1.5 g, or 7.5 g of cefuroxime. ZINACEF in the dry state should be stored between 15° to 30°C (59° to 86°F), and protected from light.

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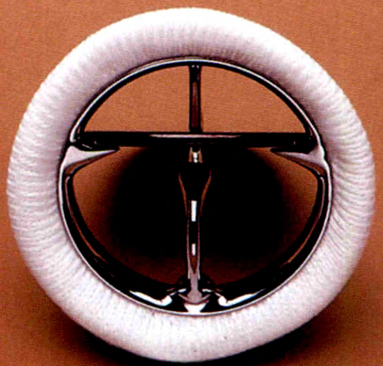

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Fact and Fiction About Management of Aortic Transection

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During the past 25 years, *The Annals of Thoracic Surgery* has contained more than 65 articles on issues surrounding blunt injury to the thoracic aorta. Incidence, prehospital management, emergency center management, technique of aortography, and natural history are covered in more than 800 published articles and book chapters. Although each year 8,000 persons in the United States sustain this injury, surgeons in most major trauma centers will see very few patients with this injury. Each thoracic surgeon will rarely, if ever, operate on patients with acute injury to the thoracic aorta. Even in series from large university centers, fewer than 50 cases are usually cited covering up to 20 years experience of six to ten different surgeons.

During the past 15 years, evolutionary concepts have polarized thoracic surgeons and unfortunately inspired lawyers to pursue these types of cases. Repeatedly quoted platitudes not supported by controlled studies include the following.

1. Shunting prevents paraplegia.
2. Use of shunting techniques will prevent a lawsuit, even if paraplegia occurs.
3. The longer the clamp time, the greater the incidence of paraplegia.
4. If the clamp time is anticipated to exceed 30 minutes, then some type of shunting should be used.
5. Clamp times less than 30 minutes reduce the incidence of paraplegia.
6. Somatosensory evoked potentials and motor evoked potentials predict which patients will develop paraplegia.
7. Use of a shunt or a pump "simplifies the operation," and is recommended for the surgeon who only occasionally operates on a traumatic tear of the thoracic aorta.

The patient seen at an emergency or trauma center and ultimately found to have a thoracic aortic injury poses special problems. This patient has multisystem injuries, each of which must be evaluated individually and then in totality with other injuries. The treating physician is faced with a negative result, even before any health care evaluator treats the patient. At the onset, outcome is adversely affected by several factors.

1. This injury usually occurs late at night when staffing and support personnel are not optimal.
2. The inadequate distribution of designated trauma centers across the United States causes patients with this injury often to be taken to a center unaccustomed or ill-equipped to provide optimal evaluation and care. This is not the fault of the hospital, but rather the fault of society and legislative bodies who have not seen fit to develop trauma systems or appropriate funds to adequately support this need.
3. Rarely will an individual surgeon have experience in the management of more than a few such injuries.

No published series prospectively compares or randomizes the various perioperative monitoring and technical aspects of the surgical management. Even in the article in this issue by Hess and associates [1], the three techniques were not performed during the same time period and were analyzed retrospectively. Due to numerous concomitant advances in operative techniques and medications, one must be very careful in drawing conclusions from retrospective historical controls.

In only 4 of the 31 cases presented in the article by Hess and associates was repair accomplished in 30 minutes or less. The average clamp time in the Houston series of acute aortic injuries was 38 minutes, with the longest being 65 minutes. Both the length of the clamp time required to achieve repair and the complication (and death rate) are functions of the complexity of the injury rather than the technical expertise of the surgeon. The frequently repeated statement that a clamp time greater than 30 minutes requires a shunt or a pump to "protect the patient from paralysis and the surgeon from lawsuit" is a fallacy. In a careful analysis of the composite data available from the literature, it is clear that both the 30-minute "golden period" and the protective potential of shunts and pumps are overstated and overemphasized. Cases of no paraplegia subsequent to clamp times in excess of 110 minutes (or even permanent total exclusion of the thoracic aorta) have been documented. Furthermore, paraplegia has been reported to occur after clamp times less than 30 minutes. Obviously, the etiology of paraplegia must rest with multifactorial causes other than clamp times, perioperative clamp, shunt, or pump management, or even monitoring techniques. Undoubtedly, the patient's individual anatomy contributes substantially to the incidence of this complication. Despite early hopes that either technical maneuvers or monitoring techniques would help to reduce its incidence after thoracic aortic operations, a 5% to 7% paraplegia rate persists.

Reforms concerning the definition of an expert witness are necessary. So-called experts include retired surgeons with very little total (and especially recent) experience

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with acute traumatic aortic transection. The suggestion that an expert witness be defined as one who has been in active practice for at least 75% of the time during the past 2 years in the same specialty as the defendant is not only logical, but essential to a fair judicial process.

The perpetual arguments on the merits or demerits of clamp/repair, temporary shunts, or cardiopulmonary bypass are exceeded only by the endless debates surrounding motor or sensory neurological evoked potentials. In truth, neither of these debates has clear, direct bearing on the usual acute traumatic transection of the thoracic aorta. None of these techniques should be condemned or championed. Excellent recent studies using each have been published. Each should be considered a standard; however, none of the techniques should be mandated. For acute trauma, the evoked potentials possibly have no practical utility. The use of the centrifugal pumps as suggested by Hess and associates is a variation of other pump bypasses with the advantage of not requiring systemic heparinization. With the current knowledge base, use of centrifugal pumps should not replace other equally successful nationally accepted techniques.

It is imperative that both surgeons and attorneys recognize the ever changing and advancing nature of trauma treatment. Currently, the use of any temporary bypass shunt, "fast" surgery, intraluminal grafts, primary repair, neuroplegic solutions (including hypothermia), somatosensory evoked potentials, motor evoked potentials, bypass pumps, spinal fluid pressure monitoring, spinal fluid removal, injection of paperverine hydrochloride into the spinal fluid, simple clamp/repair techniques, preoperative radicular artery angiography, or any other techniques have not "protected" the patient from this dread complication.

Doctor Hess and his associates are to be congratulated for presenting their small series of patients successfully managed with a relatively new adaptation of older technology. Their article should be put into the total perspective as one acceptable approach to an extremely complex injury. It should not be quoted as establishing the "preferred" or "standard" technique. To mandate a specific form of established therapy through court decisions could deny future patients the ability to have state-of-the-art interventions.

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The Arterial Switch Procedure for the Neonate: Coming of Age

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One of the most interesting chapters in the history of surgery for congenital heart disease has been the evolution of the arterial switch procedure in the treatment of transposition of the great arteries. The article by Dr Carl Backer and his associates in this issue [1] adds to our knowledge of a relatively new surgical procedure.

The stimulus for the application of the arterial switch procedure to simple transposition in the neonate was concern with the long-term results of the intraatrial baffle repair. These concerns were confirmed to some extent by two recent landmark articles on the Mustard and Senning operations. Williams and associates [2] from the Hospital for Sick Children, Toronto, "home" of the Mustard procedure, in a report with a 20-year follow-up showed that the operation could be done with a very low early mortality of only 1% and with a late mortality of only 5%. Arrhythmias, however, were common, with only 59% of patients in sinus rhythm at 10 years. Tricuspid regurgitation occurred in 4% of patients, and clinically significant right ventricular dysfunction in 10%. Baffle obstruction or leak requiring reoperation occurred in 10%. In another landmark article from the University Hospital, Zurich, "home" of the Senning procedure, Turina and co-workers [3] reported on the long-term follow-up of the Senning procedure. They found a 95% long-term survival at 9 years in patients operated on after 1978 for simple transposition. Reoperation was necessary in 6% and pacemaker insertion was required in 8% at 10 years. Tricuspid regurgitation occurred in 4%. Sudden death and late heart failure occurred in 3%. These two reports confirm the long-term sequelae and concerns about right ventricular function in patients undergoing intraatrial baffle repair for simple transposition. In addition, it is important to note that there is a mortality between birth and the performance of the intraatrial baffle repair that was 9.6% in the Toronto group's experience [2] and 5% in that of Backer and associates [1]. This must be added to the relatively low operative mortality, which has been one of the strongest arguments for the intraatrial baffle repair.

The arterial switch procedure for the neonate was first reported in 1982 [4], but was initially associated with a high operative mortality. Castaneda and associates [5] reported the first series with an acceptable operative mortality. Since then, several groups have reported excellent results with this innovative approach of immediate correction in the newborn.

Backer and associates [1] provide an interesting comparison of the arterial switch procedure and the Mustard operation for simple transposition performed in the first 3 months of life. The operative mortality was similar at 8.7% and 8.1% for the Mustard and switch procedures, respectively. It is not clear from the paper if the Mustard procedure was done electively at this early age (42 ± 31 days) or if some of these were infants doing poorly after balloon septostomy. The Toronto group [2] and others have shown that in older infants a mortality of 1% to 2% can be achieved. The experience with the arterial switch reported by the Congenital Heart Surgeons Society [6] indicates that there is a learning curve for this delicate operation and that a mortality of 5% to 10% can be achieved by an experienced group; however, in centers with a small experience, the mortality was 50%. It should be pointed out that in the so-called low-risk institutions, there was no difference in survival at 1 year between the arterial and atrial switch procedures.

The intermediate-term results reported by Backer and associates are similar to those reported by the group from Boston Children's Hospital [7]. Systemic ventricular ejection fraction was 98% ± 6% in patients undergoing arterial switch compared with 79% ± 15% in those having the Mustard procedure, and late arrhythmias occurred in only 3% of the former group versus 57% of the latter. Late survival with a follow-up of only 4.8 and 2.6 years, respectively, was similar. In the patients reported by the Boston Children's Hospital group [7], the early mortality was 7.4% in the last 2.5 years versus 13% over 5 years. Late reoperation for pulmonary stenosis was required in 5 of 49 patients (10%) followed for 29 months and 14% had occlusion of the left anterior descending coronary artery, despite which there was normal left ventricular function. Again, in both centers those children undergoing the arterial switch as neonates avoid the substantial early mortality between septostomy and delayed arterial switch.

The early and intermediate-term results of the arterial switch procedure continue to support its use as the procedure of choice for simple transposition in the neonate in those institutions that can achieve an operative mortality of between 5% and 10%. The long-term results are so far not available. Possible future problems include late aortic and pulmonary anastomotic stenosis requiring reoperation, coronary ostial stenosis, which could cause sudden death, and late aortic regurgitation. Meanwhile, the ability to do a complete anatomical repair for a complex lesion in the newborn stands as a major achievement in the annals of cardiac surgery.

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Cryoanalgesia for Postthoracotomy Pain

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Cryoanalgesia is an effective method of producing prolonged somatic nerve analgesia. When used for postthoracotomy pain management it must be remembered that cryoanalgesia is nothing more than a prolonged somatic nerve block. The pain after thoracotomy is a compilation of several factors: incisional pain, pain secondary to interruption of muscular and ligamentous structures by the retractor, and pain of plural irritation usually secondary to the chest tube. It is therefore apparent that cryoanalgesia in and of itself cannot provide 100% pain relief, although in one series complete pain relief was noted in close to 80% of patients so managed [1].

In this issue, the paper by Müller and associates [2] questions the efficacy of cryoanalgesia for postthoracotomy pain. Why the disparency in results? First one has to look at the technique of cryoanalgesia. It is necessary for the cryoprobe to be in contact with and freeze the nerve to a sufficient degree that a cryogenic lesion occurs. The characteristics of a cryogenic lesion, which can only be determined histologically, are changes in tissue osmolarity, increase in cell wall permeability, physical disruption of the myelin sheath, and vascular changes producing cellular extravasation. However, the support structure of the nerve remains intact, allowing nerve regrowth to occur within normal anatomical channels [3].

Apparently this technical aspect was done correctly. However, it is also necessary to have the chest tube emerge through the blocked dermatomes in the chest wall. In this study the chest tube came out either below or above where the cryoprobe was applied. The fact that the patient had a numb incision area did not prevent him or her from feeling this discomfort. Clinical experience has proven that just relieving one of several sites of pain that a patient might have in essence does nothing to diminish the need for medication. This is exactly what Müller and associates found.

Müller and associates also noted no differences in pain secondary to mobility or peak expiratory flow after cryoanalgesia. This is similar to what my colleagues and I have reported [4]. The reasons, of course, have to do with the other painful aspects of the postthoracotomy syndrome. When one goes from lying to sitting or tries an effort-dependent pulmonary function measurement such as peak expiratory flow, pain will be enhanced. One study [5] did note a 60% decrease in postoperative atelectasis rate in patients with cryoanalgesia versus conventional therapy. However, even these results must be questioned, as pulmonary function testing and blood gases were not obtained to confirm the diagnosis.

Perhaps the most disturbing portion of the paper by Müller and associates was the incidence of postthoracotomy dysesthesias, which started 6 weeks postoperatively. I have heard others talk of this complication, although in our experience we have had only 1 such case that I am aware of. One asks the question, however, whether the dysesthesias are secondary to the cryolesion because the histological studies, done on animals, show restoration of function without the presence of neuromas. Nerve regeneration appears normal. One explanation for postthoracotomy dysesthesias is that once the cryolesion block begins to dissipate the injury done to nerves during the operation may become apparent. Another possibility is that the reported dysesthesias are nothing more than an exaggerated Tinel's sign seen when nerves regenerate. Why there is such a high incidence in the paper by Müller and associates I am not certain.

Cryoanalgesia is an integral part of our postthoracotomy management. We, in addition, use epidural narcotic administration for the first couple of days postoperatively to cover other aspects of the postthoracotomy pain syndrome. Observation of these patients in the postanesthetic or intensive care units and on the ward reveals that patients are almost devoid of serious postoperative pain.

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Traumatic Tears of the Thoracic Aorta: Improved Results Using the Bio-Medicus Pump

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Traumatic disruption of the descending thoracic aorta is a relatively rare but dramatic injury. Controversy remains regarding the use of shunts during operative repair. Discouraged by our results using the "no shunt" technique, we adopted the recently reported technique using the Bio-Medicus pump for left atrium–femoral artery bypass without heparin sodium. At Charlotte Memorial Hospital and Medical Center, 39 patients were treated for tears of the descending thoracic aorta between January 1979 and October 1988. Eight patients died before repair could be completed. Four patients underwent repair using femorofemoral bypass with 1 death and no instances of paraplegia. Fifteen patients had repair using the no-shunt technique with 4 deaths and three instances of paraplegia. Since January 1986, 12 patients have been treated using the Bio-Medicus heparinless pump with no deaths and no instances of paraplegia. We present our experience to confirm the reports of others regarding the efficacy of this technique. We believe it reduces the morbidity and mortality associated with this serious injury and aids in the hemodynamic management of the patient during aortic clamping.

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Traumatic disruption of the descending thoracic aorta is an infrequently encountered but potentially lethal injury. The techniques of patient management are generally agreed on, but controversy persists regarding the surgical techniques; specifically, to shunt or not to shunt.

The report by Oliver and associates [1] describing their results with use of the Bio-Medicus centrifugal pump (Bio-Medicus, Eden Prairie, MN) led us to adopt their technique. Impressed with our seemingly better results with this method compared with previous techniques, we conducted a retrospective review of all patients with traumatic injuries of the descending thoracic aorta seen at Charlotte Memorial Hospital and Medical Center since January 1979.

Material and Methods

Between January 1, 1979, and October 1, 1988, 39 patients were treated for traumatic injuries of the descending thoracic aorta. They ranged in age from 16 to 70 years with a mean age of 32 years. There were 29 male and 10 female patients. Twenty-six patients were transferred to Charlotte Memorial Hospital from surrounding hospitals within a radius of 112 km. Thirteen patients were taken directly to our emergency room from the scene of the accident. Thirty patients were injured in automobile accidents, 4 in falls, 3 in motorcycle accidents, 1 as a pedestrian, and 1 after striking a tree limb while riding horseback.

The patients were divided into four groups based on the method of treatment. Group 1 included 8 patients who did not undergo grafting. They died before it could be completed. Group 2 included 4 patients operated on with the aid of femorofemoral bypass. Group 3 comprised 15 patients operated on without the aid of a shunt and Group 4, 12 patients having operation with the aid of left atrium–femoral artery bypass using a Bio-Medicus pump without heparin sodium.

All patients were managed with careful attention preoperatively to acid-base balance, volume status, and respiratory variables. Control of intraabdominal bleeding took precedence over arteriography or thoracotomy. Computed tomography was performed before thoracotomy if intracranial bleeding was suspected. Double-lumen endotracheal tubes were used in all patients, and right radial artery lines were inserted for blood pressure measurement. The Haemonetics Cell Saver system was used in all procedures. Patients treated with femorofemoral bypass or left atrium–femoral artery bypass also had right femoral artery lines placed. Roller pumps, systemic heparin, and bubble oxygenators were used for femorofemoral bypass.

In group 4 patients, the left common femoral artery was exposed before thoracotomy. After thoracotomy, an incision in the pericardium anterior to the phrenic nerve was utilized to expose the left atrial appendage, which was encircled with a pursestring suture. A 28F or 32F wired venous cannula was inserted into the left atrial appendage, and the Bio-Medicus pump head was primed by

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Table 1. Causes of Death in 8 Patients Who Died Before Grafting Could Be Completed

Cause	No. of Patients
Closed head injury	1
Failure to gain proximal control	2
Ventricular fibrillation during thoracotomy	1
Combined hemoperitoneum and hemothorax with exsanguination	3
Exsanguination into right chest during left thoracotomy	1

Table 2. Complications in Groups 3 and 4

Complication	No Shunt (n = 15)	Bio-Pump (n = 12)
Death	4	0
Paraplegia	3	0
Renal failure	4	0
Respiratory failure	4	3
Sepsis	2	1
None	6	6

gravity drainage. The femoral artery connection was completed, and the pump flow was initiated at 1.0 to 1.5 L/min and increased to as high as 3 L/min during clamping. Mean pressures in the lower extremities were kept at 50 to 70 mm Hg. Upper extremity pressure was maintained at normal levels by increasing or decreasing pump flow. Dacron grafts with end-to-end anastomoses were inserted in all 31 patients in groups 2 through 4.

Results

All 8 patients in group 1 died before grafting could be completed. The cause of death is summarized in Table 1. The patient with the severe head injury never underwent operation, and was pronounced brain dead 48 hours after injury. The remaining 7 patients died during thoracotomy or combined laparotomy and thoracotomy of exsanguination (6 patients) and ventricular fibrillation (1 patient).

The 4 patients in group 2 underwent operation with femorofemoral bypass and full heparinization. A 79-year-old man died of low cardiac output, cardiac arrhythmias, and coagulopathy within 48 hours after operation. The remaining patients survived without neurological problems.

Table 2 summarizes the complications in groups 3 and 4. If the 4 patients in group 2 are combined with the 12 patients in group 4, there was but 1 death and no cases of paraplegia or renal failure among the 16 patients with a shunt. Among the 15 patients without a shunt (group 3), there were 4 deaths, 3 cases of paraplegia, and 4 cases of renal failure. Three of the 4 patients with renal failure required dialysis, and only 1 survived. The cause of death in the patients receiving a graft is shown in Table 3.

Aortic cross-clamp times were evaluated. Longer clamp times were associated with more serious complications, but more importantly, only 4 of the 31 patients underwent repair in 30 minutes or less (Table 4). The clinical features of the 8 patients with clamp times of 51 minutes or longer were evaluated and are summarized in Table 5. Among these 8 patients, 3 of the 4 without a shunt died compared with only 1 of 4 operated on with the aid of a shunt.

The 3 patients with paraplegia (group 3) had clamp times of 28, 38, and 60 minutes. There were 2 additional patients with paraparesis (clamp times, 26 and 33 minutes), but both had had a previous laminectomy and symptoms of paresis involving the lower extremities.

The overall mortality in our series was 33% (13/39). Six (67%) of 9 patients aged 60 years or older died, and 4 of these 6 were injured in falls from rooftops or trees. Five (16%) of the 31 patients with a graft died, and 4 (27%) of the 15 patients without a shunt died. Associated injuries were similar for all patients undergoing grafting.

Comment

The morbidity and mortality associated with traumatic injuries of the thoracic aorta are generally related to the severity of the injury. For patients who reach the hospital and undergo operative repair, it has been stated that repair without a shunt can be expected to produce results

Table 3. Causes of Death in Patients Receiving a Graft

Patient No.	Age (yr)	Shunt	Clamp Time (min)	Cause of Death
6	40	None	51	Multiple-organ failure, renal failure (dialysis), respiratory failure
7	37	None	90	Multiple-organ failure, renal failure (dialysis), cardiac arrest during clamping
13	79	Femorofemoral bypass	52	Low cardiac output, cardiac arrhythmias, coagulopathy; reexplored for bleeding
15	73	None	70	Closed head injury; pronounced dead 48 h after repair
37	67	None	35	Intraabdominal and pulmonary sepsis, perforated duodenal ulcer and gangrenous gallbladder (mild renal failure)

Table 4. Clamp Times and Complications in 31 Patients

Clamp Time (min)	No. of Patients	Complications
21–30	4	Death, 1; paraplegia, 1; renal failure, 0
31–40	9	Death, 1; paraplegia, 1; renal failure (mild), 1
41–50	10	Death, 0; paraplegia; 0; renal failure, 0
51–60	3	Death, 2; paraplegia, 1; renal failure, 2
61–120	5	Death, 2; paraplegia, 0; renal failure, 1

equal to those obtained with a shunt if the clamp time is approximately 30 minutes or less [2–4].

Our experience indicates that in this group of critically ill patients, unexpected events such as cardiac arrhythmias and fibrillation, technical difficulties with extensive proximal injury, and unexpected blood loss can lead to prolongation of the aortic cross-clamp time. Preoperative hypotension, shock, blood loss, and pulmonary dysfunction increase the susceptibility of organs to further ischemia induced by cross-clamping. Renal and hepatic failure and, in some instances, paraplegia can be expected to occur even without interruption of critical collaterals during repair. In our series, only 4 of 31 patients underwent repair in less than 30 minutes. The average clamp time for patients having operation without a shunt was 43 minutes and for patients operated on with a shunt, 48 minutes. Because of these findings, we, like others [1], now favor left atrium–femoral artery bypass rather than the no shunt technique. Although excellent results have been obtained with the use of femorofemoral bypass with systemic heparinization [5], the risk of bleeding, especially in patients with serious intracranial injuries and large retroperitoneal hematomas, makes it potentially more dangerous.

Two excellent reviews [4, 6] regarding spinal cord ischemia suggest that multiple factors contribute to cord ischemia. These include hypotension, simple aortic clamping, increased cerebrospinal fluid pressure, and sacrifice of important intercostal collaterals. All but the last can be favorably influenced by maintenance of adequate flow and pressure to the distal aorta and prevention of upper extremity hypertension by mechanical rather than pharmacological unloading. If one assumes that all cases of paraplegia following repair of descending thoracic aortic injuries are related to interruption of critical spinal cord blood supply, then shunting would be of no value. We are not convinced that this is the case; therefore, measures to enhance the blood flow and pressure to the occluded aorta seem indicated.

The Bio-Medicus centrifugal pump and left atrium–femoral artery bypass have been shown both clinically [1] and experimentally [7] to provide easily regulated flow and pressure to the clamp-occluded distal aorta. The pump is inflow dependent and resistance dependent, and does not require a reservoir. Also, attempts in our laboratory to pump air through the system were unsuccessful.

Although the measurement of somatosensory evoked potentials has not been shown to alter the outcome of operations for thoracic and thoracoabdominal aneurysms [8], it has proved helpful in detecting spinal cord ischemia [9]. False-negative and false-positive results have been noted as well as their alteration by specific anesthetic agents. The development of techniques for assessment of anterior spinal cord function (motor evoked potentials) combined with maintenance of lower extremity perfusion should enable the surgeon to detect those patients who

Table 5. Outcome for 8 Patients With Prolonged Cross-Clamp Times

Patient No.	Age (yr)	Clamp Time (min)	Shunt	Outcome
4	71	60	None	Alive: paraplegia, renal failure (dialysis), respiratory failure (prolonged ventilation)
6	40	51	None	Death: renal failure, dialysis, pulmonary failure
7	37	90	None	Death: renal failure, multiple-organ failure, sepsis, hepatic failure, dialysis, cardiac arrest during clamping
13	79	52	Femorofemoral bypass	Death: low cardiac output, cardiac arrhythmias, coagulopathy
15	73	70	None	Death: brain death 48 h after operation, neurologic function never tested
20	21	93	Femorofemoral bypass	Alive: no major complications
23	26	120	Bio-Medicus	Alive: ventricular fibrillation during clamping, difficult proximal repair, multiple-system injuries
28	55	63	Bio-Medicus	Alive: vocal cord paralysis, 6 days on ventilator

have ischemia during clamping and require rapid restoration of flow or reimplantation of critical collaterals [6]. These measures have not been effective to date, especially in patients with traumatic injuries.

The complete prevention of paraplegia may not be possible. Past attempts to prolong the safe period of ischemia by the use of hypothermia [10] were associated with complications that prevented their acceptance. Recent experimental work [7] involving the Bio-Medicus centrifugal pump and regional hypothermia seems very promising.

Primary repair of thoracic aortic injuries has been advocated in an effort to reduce clamp time and avoid placement of prosthetic material [11, 12]. This is most easily accomplished in cases of incomplete transection of the aorta. In our experience, most injuries involve complete separation of the transected ends. Two patients with ascending aortic tears had quick and easy repair with this technique. Clamp times were short but of no consequence.

In conclusion, we have found use of the Bio-Medicus centrifugal pump and left atrium–femoral artery bypass to be a safe and simple method of distal perfusion for operations on the thoracic aorta. The pump can be used without heparin and provides adequate blood flow and pressure to the distal aorta and intraabdominal organs. It is easily regulated and reduces upper body hypertension without the use of potentially harmful vasodilating agents. Combined with provisions to salvage lost blood, this technique provides the surgeon with the tools to deal with the difficult technical problems and unexpected events that frequently accompany these injuries. It also eliminates the sense of urgency that is present when no shunting procedures are used.

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Transposition of the Great Arteries: A Comparison of Results of the Mustard Procedure Versus the Arterial Switch

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Sixty infants with transposition of the great arteries and intact ventricular septum underwent primary surgical correction in the first 3 months of life. Twenty-three patients had a Mustard procedure (group 1) and 37 patients, an arterial switch operation (group 2). The mean age at the time of repair was 42 ± 31 days for group 1 and 8 ± 6 days for group 2 ($p < 0.001$). The mean weight at the time of repair was 3.6 ± 0.7 kg for group 1 and 3.4 ± 0.5 kg for group 2 (p = not significant). Operative mortality was 8.7% (2/23) in group 1 and 8.1% (3/37) in group 2 (p = not significant). The incidence of arrhythmias in the early postoperative period was 39% (9/23) in group 1 and 11% (4/37) in group 2 ($p < 0.01$). All patients were followed a mean of 4.8 ± 2.4 years in group 1 and 2.6 ± 1.4 years in group 2 ($p < 0.001$). Postoperative catheterization has been performed in 86% (18/21) of group 1 operative survivors and 50% (17/34) of group 2 operative survivors. Ejection fraction of the systemic ventricle was 79% ± 15% of predicted normal in group 1 and 98% ± 6% in group 2 ($p < 0.005$). The incidence of late arrhythmias was 57% (12/21) in group 1 and 3% (1/34) in group 2 ($p < 0.001$). There have been 2 late deaths in group 1 and 1 late death in group 2 (p = not significant). The data suggest that the arterial switch operation has early and late mortality comparable with those of the Mustard operation but is superior in terms of significantly fewer arrhythmias and preservation of ventricular function, thus making it the procedure of choice for infants with transposition of the great arteries.

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At present, there are two options for surgical correction in infants born with transposition of the great arteries and intact ventricular septum: a venous rerouting procedure such as a Mustard [1] or Senning [2] operation, or an arterial switch operation [3]. Although the trend in many institutions has been toward the arterial switch operation [4], others believe that venous rerouting is still the procedure of choice [5–7]. Because of this ongoing controversy, we elected to retrospectively compare our results obtained with the Mustard procedure versus the arterial switch operation.

To assess two groups of patients who were most comparable, we chose to examine infants with complete transposition of the great arteries with intact ventricular septum who had one-stage physiological or anatomical correction within the first 3 months of life (100 days). The selection of this group was based on the recently reported excellent results with venous switch operations in this particular age group against which other techniques of transposition repair bear comparison [8, 9]. Specifically, we chose to compare early mortality, length of hospital stay, early and late results and complications, incidence of early and late arrhythmias, results of postoperative catheterization including ventricular function, and long-term mortality.

Material and Methods

Among 290 children with transposition of the great arteries treated surgically at The Children's Memorial Hospital in Chicago from 1968 to 1988, 214 had the Mustard operation and 76, an arterial switch procedure. Sixty children were operated on within the first 3 months (100 days) of life and had an intact ventricular septum or small ventricular septal defect not requiring closure at the time of repair, and they form the basis for this study.

Twenty-three of the 60 infants had a Mustard operation (group 1) and 37, an arterial switch (group 2) (Table 1). All patients had primary repair without prior surgical palliation or preparation. The same surgical team operated on both groups. All patients in group 1 had cardiac catheterization and balloon atrial septostomy before the Mustard operation, and 26% received prostaglandins. Twenty-nine (78%) of the 37 patients in group 2 had cardiac catheterization and balloon atrial septostomy before the arterial switch, and 92% received prostaglandins. Eight infants (22%) (7 of the last 9 in the series) in group 2 underwent operation on the basis of the preoperative echocardiogram.

For group 1, age at the time of repair ranged from 4 to

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Table 1. Patient Population[a]

Variable	Group 1, Mustard (n = 23)	Group 2, Switch (n = 37)	p Value
Male	18 (78)	28 (76)	NS[b]
Prostaglandin E_1	6 (26)	34 (92)	<0.005[b]
Catheterization[c]	23 (100)	29 (78)	NS[b]
Age range (days)	4–96	1–34	
Mean age (days)	42 ± 31	8 ± 6	<0.001[d]
Mean weight (kg)	3.6 ± 0.7	3.4 ± 0.5	NS[d]

[a] Numbers in parentheses are percentages. [b] This is by χ^2 test. [c] This means cardiac catheterization with balloon atrial septostomy. [d] This is by two-tailed Student's t test.

NS = not significant.

96 days (mean age, 42 ± 31 days), and the mean weight was 3.6 ± 0.7 kg. For group 2, age at the time of repair ranged from 1 to 34 days (mean age, 8 ± 6 days), and the mean weight was 3.4 ± 0.5 kg ($p < 0.001$ and p = not significant [NS], respectively, versus group 1). Seventy-eight percent of the patients in group 1 and 76% of the patients in group 2 were male.

Results were analyzed using the two-tailed Student's t test. A p value of less than 0.05 was considered significant.

Results

Early Results

There were 2 operative deaths in group 1, a mortality rate of 8.7% (Table 2). The first patient who died (the 12th in the group) was a 17-day-old girl weighing 2.7 kg. Renal failure necessitating peritoneal dialysis developed postoperatively, and she died on the ninth postoperative day of peritonitis and sepsis. The second patient who died (the 16th in the group) was a 3-month-old boy weighing 4.3 kg. He had arrhythmias and low cardiac output, and died on the second postoperative day. At autopsy, thickened, stenotic tricuspid and mitral valves were found.

In group 2 there were 3 operative deaths, a mortality rate of 8.1% (p = NS versus group 1). Two deaths occurred early (the eighth and tenth patients). The first patient who died was a 14-day-old boy weighing 2.5 kg (lowest weight in the series). He had poor ventricular function preoperatively (left ventricular ejection fraction, 67% of predicted normal). Injury to the left coronary artery by a cardioplegia cannula contributed to the death. The second death occurred in a 7-day-old boy who weighed 3.2 kg. He died suddenly on the seventh postoperative day. The results of autopsy were not revealing. The third patient who died was a 3-day-old boy weighing 2.6 kg whose left ventricular mass was only 65% of predicted normal and who required extracorporeal membrane oxygenator support for seven days after operation. He died of sepsis on the 20th postoperative day.

The length of postoperative hospital stay and incidence of arrhythmias, infections, and seizures are outlined in Table 2. In group 1, there were 3 patients (13%) with postoperative atrial arrhythmias, 1 (4.3%) with ventricular arrhythmia, and 5 (22%) with atrioventricular dissociation, a total incidence of early arrhythmias of 39%. In group 2, on the other hand, 2 patients (5%) had atrial arrhythmias and 2 had temporary atrioventricular dissociation, a total incidence of early arrhythmias of 11% ($p <$ 0.01 versus group 1).

Four patients (17%) in group 1 had postoperative infections. Two patients were given a course of antibiotics for positive blood cultures and a clinical diagnosis of sepsis. One patient had peritonitis and another, mediastinitis necessitating repeat sternotomy with debridement. In group 2, 2 patients (5%) had postoperative infections (p = NS versus group 1). One had a minor wound infection, and 1 had sepsis leading to death after extracorporeal membrane oxygenator support.

Four patients (17%) in group 1 had postoperative seizures. In group 2, 11 patients (30%) had postoperative seizures (p = NS). In all instances, seizures were thought to be metabolic in origin and were easily controlled with anticonvulsants. None of these patients have long-term neurological sequelae except an infant who had an arterial switch and is developmentally delayed (the first patient operated on in this group, who had a stormy postoperative course).

Late Results

There have been 2 late deaths (9.5%) among the 21 operative survivors in group 1 (Table 3). The ninth patient in the series was known to have right ventricular dilatation and intermittent atrioventricular dissociation with a junctional escape rhythm. He died suddenly at home 5 years after repair. The 19th patient in the series had severe right ventricular dysfunction (right ventricular ejection fraction, 42% of predicted normal) and also died suddenly at home 1.5 years after repair.

There has been 1 late death (3.0%) among the 34 operative survivors in group 2 (p = NS versus group 1). The second patient in the series had right bundle-branch block and died suddenly at home 3.5 years after operation.

The patients in group 1 have been followed for 1 to 9 years. Patients in group 2 have been followed between 1

Table 2. Early Results[a]

Variable	Group 1, Mustard (n = 23)	Group 2, Switch (n = 37)	p Value
Death	2 (8.7)	3 (8.1)	NS[b]
Hospital stay (days)			
Range	5–30	4–21	
Mean	13.5 ± 7.5	10.5 ± 4.8	NS[c]
Arrhythmia	9 (39)	4 (11)	<0.01[b]
Infection	4 (17)	2 (5)	NS[b]
Seizures	4 (17)	11 (30)	NS[b]

[a] Numbers in parentheses are percentages. [b] This is by χ^2 test. [c] This is by two-tailed Student's t test.

NS = not significant.

Table 3. Late Results[a]

	Group 1, Mustard (n = 21)	Group 2, Switch (n = 34)	p Value
Death	2 (9.5)	1 (3)	NS[b]
Follow-up			
Range (yr)	1–9	0.1–5	
Mean (yr)	4.8 ± 2.4	2.6 ± 1.4	<0.001[c]
Reoperation	2 (9.5)	0	NS[b]
Pacemaker	1 (4.8)	0	NS[b]
Arrhythmia	12 (57)	1 (3)	<0.001[b]

[a] Numbers in parentheses are percentages. [b] This is by χ^2 test. [c] This is by two-tailed Student's t test.

NS = not significant.

month and 5 years. The mean follow-up for group 1 patients is 4.8 ± 2.4 years, significantly longer than that for group 2 patients, 2.6 ± 1.4 years ($p < 0.001$).

Two patients in group 1 have required reoperation (2/21 or 9.5%), 1 for baffle leak and 1 for superior vena cava obstruction 1 and 2 years, respectively, after the Mustard procedure. One patient in group 1 (4.8%) required pacemaker placement for atrioventricular dissociation.

Twelve (57%) of the 21 operative survivors in group 1 have late arrhythmias. Eight (38%) have atrial arrhythmias (sick sinus syndrome and junctional rhythm), 1 (5%) has ventricular arrhythmia, and 3 (14%) have atrioventricular dissociation. Only 9 patients (43%) are currently in normal sinus rhythm.

There have been no reoperations in group 2. In regard to arrhythmia, only 1 patient (3.0%) in group 2 was treated for 6 months for late nonsustained ventricular tachycardia. His medication was discontinued 2 years ago. All patients in group 2 are currently in normal sinus rhythm. The incidence of late postoperative arrhythmias is significantly higher in group 1 (57%) compared with group 2 (3%) ($p < 0.001$).

Eighteen (85%) of the 21 operative survivors in group 1 have had postoperative catheterization 2 to 44 months (mean time, 19 months) postoperatively compared with 17 (50%) of the 34 operative survivors in group 2 (range, 10 to 25 months; mean time, 14.9 months) (Table 4). Variables of systemic ventricular function (right ventricle in group 1 and left ventricle in group 2), ie, systemic ventricular end-diastolic volume (percent of normal) and systemic ventricular ejection fraction (percent of normal), were compared [10]. The mean systemic ventricular end-diastolic volume in group 1 was 133% ± 33% (95% confidence limits, 83.8% to 116.2%). In group 2, the systemic ventricular end-diastolic volume was 115% ± 23% (95% confidence limits, 84.5% to 115.5%) (p = NS). In contrast, the systemic ventricular ejection fraction in group 1 was a mean of 79% ± 15% (95% confidence limits, 89.3% to 110.7%) compared with 98% ± 6% (95% confidence limits; 91.3% to 108.7%) for group 2 ($p < 0.005$).

In group 1, 6 of 18 patients had mild to moderate tricuspid insufficiency. In Group 2, 15 of 17 patients had mild pulmonary stenosis and 8 of 17 patients, mild pulmonary insufficiency. The mean pressure difference between the right ventricle and the pulmonary artery for those with pulmonary stenosis was 15.5 ± 4.9 mm Hg (range, 8 to 25 mm Hg). None of the patients had evidence of aortic stenosis, and 6 of 17 patients had trivial aortic insufficiency.

Comment

Attempts to perform the arterial switch operation for transposition of the great arteries in the early 1960s were unsuccessful [11]. More recently, because of the encouraging results reported by Jatene and colleagues [3] and Yacoub [12], there has been renewed interest in performing anatomical correction despite apparently satisfactory early results from the Mustard and Senning operations [5, 6]. The main reason for this shift is the ever-increasing number of reports citing a disappointingly high incidence of long-term complications of venous rerouting procedures, including arrhythmias and progressive right ventricular dysfunction [13, 14].

The present study attempts to evaluate the intermediate-term and long-term results of both arterial and venous switch operations in two comparable series of patients operated on in infancy (less than 100 days of age) by the same surgical team at the same institution. The patient populations were similar in regard to male/female ratio, percentage having cardiac catheterization and balloon atrial septostomy, and mean weight at the time of operation. The Mustard group, however, was slightly older and underwent repair at an earlier date compared with the arterial switch patients.

One of the originally cited major drawbacks of the arterial switch operation was the high early operative mortality, ranging from 30% to 50% [15, 16]. As experience with this procedure increased, operative mortality has decreased to very acceptable levels—6% in the low-risk institutions of the Congenital Heart Surgeons Society study [17] and 5.4% in the recent 110-patient series of Planche and colleagues [18]. Although operative mortality was similar for both procedures in our experience, there was a progressive decrease in the mortality rate in the anatomical correction group, with only 1 death in the last 27 patients (3.7%) in contrast to 2 deaths in the first 10 patients. If this trend continues, the mortality rate for

Table 4. Postoperative Catheterization[a]

Variable	Group 1, Mustard (n = 21)	Group 2, Switch (n = 34)	p Value
No. of patients	18 (86)	17 (50)	<0.025[b]
SVEDV (% of normal)	133 ± 33	115 ± 23	NS[c]
SVEF (% of normal)	79 ± 15	98 ± 6	<0.005[c]

[a] Numbers in parentheses are percentages. [b] This is by χ^2 test. [c] This is by two-tailed Student's t test.

NS = not significant; SVEF = systemic ventricular ejection fraction (right ventricle for group 1 and left ventricle for group 2); SVEDV = systemic ventricular end-diastolic volume (right ventricle for group 1 and left ventricle for group 2).

anatomical correction could approach 3% to 5%, which compares very favorably with that reported for the venous switch operation performed in early infancy [8, 9]. In addition, arterial switch performed in the first 1 to 2 weeks of life avoids the substantial mortality (5%) of children with transposition of the great arteries awaiting elective Mustard and Senning operations [19]. The incidence of early complications such as postoperative seizures, infection, and length of hospital stay were similar in our two groups.

Arrhythmias have been a major late complication of patients undergoing the Mustard operation [20]. They consist chiefly of atrial tachycardias, atrioventricular dissociation, and junctional rhythms, which tend to become more prevalent and severe with time. Hayes and Gersony [13] showed that of 95 patients who underwent a Mustard procedure, only 20% had atrial arrhythmias at the time of discharge, but 75% had atrial rhythm disorders by the sixth postoperative year. Deanfield and associates [21] found that in 100 patients who underwent either the Mustard or Senning operation, gradual loss of sinus rhythm occurred; at a mean of 7 years after operation, only 56% of the patients having the Senning operation and 66% having the Mustard procedure were in stable sinus rhythm.

These arrhythmias are thought by Edwards and Edwards [22] to be due to dissection around the sinus node with fibrosis in this area or sinoatrial nodal artery thrombosis and interruption of intraatrial communications by the baffle suturing. In our series, more than half of the patients who underwent the Mustard operation have serious late arrhythmias. In contrast, the arrhythmias in the arterial switch group are nearly all temporary, and, on intermediate-term follow-up, all patients in this group are in normal sinus rhythm without medication. Such a low incidence of arrhythmias is a major benefit of the arterial switch procedure compared with the Mustard procedure. Our only qualification to this conclusion is that the mean follow-up of group 2 (2.6 years) is not as long as that of group 1 (4.8 years).

The other major complication with the Mustard procedure is late systemic ventricular (right ventricular) dysfunction. The right ventricle is not morphologically intended to act as the systemic ventricle, and in patients who undergo the Mustard procedure, it tends to dilate and perform less vigorously with time [14]. Once such dysfunction sets in, it is progressive and can lead to cardiac failure [unpublished results]. The results of routine postoperative catheterization tend to confirm findings in other studies. Although there was no significant difference in the end-diastolic volume between the two groups, the ejection fraction of the systemic ventricle after the Mustard procedure was significantly lower than after the arterial switch operation. Moreover, patients after the Mustard procedure had a high incidence (33%) of systemic atrioventricular valve (tricuspid) regurgitation, presumably caused by a dilated, poorly functioning right ventricle.

There are potential complications of the arterial switch operation, for example, stenosis of the aortic, pulmonary, or coronary artery anastomosis and aortic or pulmonary valve insufficiency or stenosis. However, these complications have been rare. In our study, postoperative catheterization in the arterial switch group showed the aortic and pulmonary valves to be functioning well in the majority of patients. There was no aortic stenosis and only a low incidence of trivial aortic insufficiency. Most patients had mild pulmonary stenosis, which was hemodynamically not significant. There was no evidence of suture line stenosis in any of these patients. Longer follow-up will be necessary to define the incidence and importance of any of these complications.

In conclusion, for infants with transposition of the great arteries and intact ventricular septum, arterial switch and venous rerouting have the same early and late mortality. However, the arterial switch operation has a significantly lower incidence of early and late arrhythmias and is not associated with long-term systemic ventricular dysfunction. Early anatomical correction is the procedure of choice for children with transposition of the great arteries.

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Intraoperative Cryoanalgesia for Postthoracotomy Pain Relief

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In a randomized study, 63 patients were investigated for the benefits of cryoanalgesia after thoracotomy. Analgesia and its dependent effects such as enhancement of mobility, respiratory function, and reduced need of narcotics were evaluated. No significant differences in these variables were observed between the cryoanalgesia group and the control group. However, moderate to severe neuralgia was found in a number of patients in the cryoanalgesia group in the late postoperative period. Cryoanalgesia for pain relief after thoracotomy is not recommended.

(Ann Thorac Surg 1989;48:15–8)

Postoperative pain after a thoracic surgical procedure deserves special attention because painfully restricted respiration can have deleterious consequences (eg, respiratory failure from superficial breathing excursions, sputum retention, and bronchopneumonia). Opiates are administered for this condition, particularly in the early postoperative period, but have the disadvantage of causing a more or less pronounced respiratory depression.

From the particular anatomical placement of the lateral incision for opening the thorax parallel to the segmental innervation of the chest wall, it appears possible to provide local relief of pain by blocking the intercostal nerves at the incision. The means of achieving this type of local analgesia after thoracotomy and whether they are superior to systemic administration of analgesics have been studied [1–5].

The various methods used to this end were augmented by Nelson and associates [6] in 1974 with the introduction of cryoanalgesia. The application of cold directly to the nerves causes localized destruction of the axons while preserving the endoneurium, thereby inducing a temporary pain block in such a way as to permit subsequent problem-free regeneration of the nerve fibers. This requires local freezing of the nerves at a temperature of approximately −60°C by means of a nitrous oxide–cooled cryoprobe while making use of the Joule-Thomson effect.

To date, published studies on the subject of cryoanalgesia after thoracotomy mainly report a very beneficial analgesic effect on the postoperative course [7–10]. In none of these publications, however, was the effect of cryoanalgesia tested on a sufficiently large patient population using the standard methodical criteria for evaluation of new therapies. In the present randomized, double-blind study (patient and investigators did not know the type of therapy), a number of variables were used to compare the effect of cryoanalgesia with that of a solely systemic administration of analgesics.

Material and Methods

The study was conducted with 63 patients, aged 23 to 78 years, who gave informed consent. The study was submitted to the Committee for the Evaluation of Medical Experiments of Innsbruck University and found to be ethically unobjectionable (Innsbruck, June 14, 1985).

The patients were divided into three subgroups on the basis of surgical treatment: pneumonectomy; lobectomy or bilobectomy; and exploratory thoracotomy, parietal pleurectomy, and parenchymal resection to the extent of a segmental resection. In all patients, surgical access was obtained through a posterolateral thoracotomy in the fifth intercostal space.

The patients in the three subgroups were randomly divided into two treatment groups before the thorax was closed: cryoanalgesia and control. In the cryoanalgesia group, four intercostal nerves (one level with the thoracotomy, one a segment further cranial, and the two adjacent caudal) were exposed paravertebrally, lifted with a nerve hook, and frozen at two close sites with a nitrous oxide–cooled cryoprobe (Erbe Elektromedizin, Tübingen, Federal Republic of Germany) until a ball of ice formed around the entire nerve. In the control group, no sham operation was performed on the pertinent nerves. The thorax drainage lines were brought out in the usual location at the lowest point of the pleural cavity and, when necessary, in the second intercostal space.

Postoperative analgesic treatment involved intramuscular administration of standardized individual doses of an opiate (methadone hydrochloride) and a nonopiate compound (propyphenazone + barbiturate + caffeine [Inalgon]) as needed. To determine the analgesic effect and any possible differences between the two treatment groups, the following variables were recorded on postoperative days 1, 2, 3, 5, and 7 by a doctor who did not know the random group distribution:

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Table 1. Patient Groups by Type of Operation and Pain-Relief Therapy

Treatment Group	Exploratory Thoracotomy[a]	Lobectomy/ Bilobectomy	Pneumo- nectomy	Total
Cryoanalgesia	11	17	2	30
Control	10	18	5	33
Total	21	35	7	63

[a] Surgical treatment included exploratory thoracotomy, parietal pleurectomy, and parenchymal resection to the extent of a segmental resection.

1. Subjective pain sensation, expressed on a scale of 0 through 4 (no pain to severe pain).
2. Painfully reduced mobility when going from a lying position to a sitting position with the help of a trapeze, expressed on a scale of 1 through 5 (sitting up impossible to sitting up possible without effort).
3. Analgesic consumption of opiates and nonopiates, recorded as the total daily dose and the number of individual doses.
4. Peak expiratory flow, as an indication of the ability to cough up phlegm, measured with a mini-Wright peak flowmeter (Airmed; Clement Clark International Ltd, London, United Kingdom) and given as percentage of preoperative value.

Statistical evaluation was performed with the SPSS program package [11] using an IBM XT personal computer. Data description was performed with the FREQUENCIES and CROSSTABS procedures [11]. The Wilcoxon-Mann-Whitney test [12] (NPAR TEST procedure [11]), was used to examine the significance of the treatment differences in the framework of the final statistics. The level of significance was set at 5%.

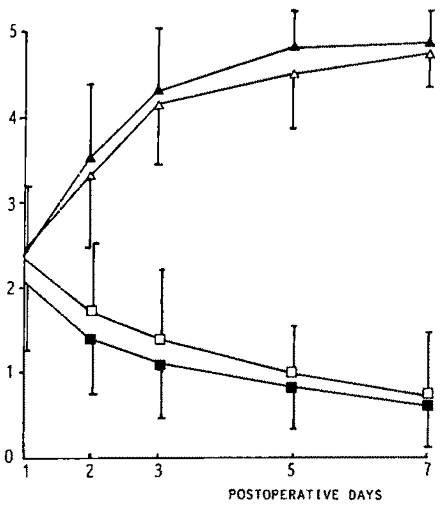

Fig 1. Pain and mobility in the postoperative course. Pain in the cryoanalgesia (■) and control (□) groups was classified on a scale of 0 to 4 (0 = none, 1 = light; 2 = moderate; 3 = strong; 4 = severe). Mobility in the cryoanalgesia (▲) and control (△) groups was classified on a scale of 1 through 5 (1 = none; 2 = with help; 3 = with strong effort; 4 = with light effort; 5 = with no effort). Data are shown as the mean ± the standard deviation.

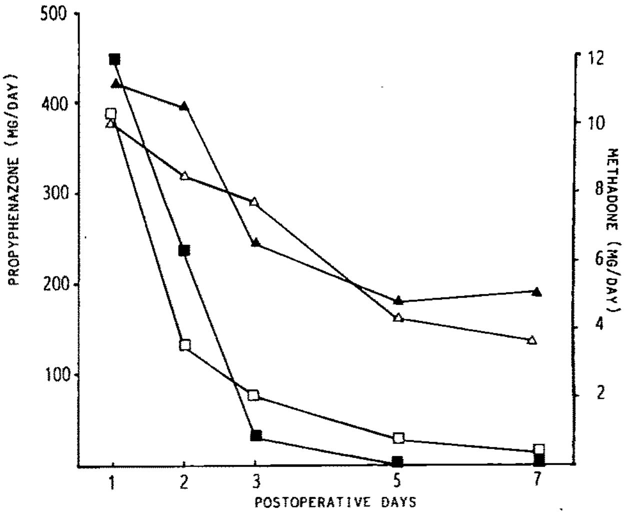

Fig 2. Consumption of analgesics. Mean use of methadone in the cryoanalgesia (■) and control (□) groups and of the nonopiate propyphenazone in the cryoanalgesia (▲) and control (△) groups during the postoperative period.

Results

Patient grouping by type of operation and pain-relief therapy is shown in Table 1. Age (cryoanalgesia group: range, 24 to 74 years, mean, 56 years; control group: range, 23 to 78 years, mean, 69 years; overall: range, 23 to 78 years, mean, 57 years) and sex were evenly distributed.

Figure 1 presents the postoperative subjective pain sensation and, complementary to this, the painfully reduced mobility when sitting up from a lying position. Graphic demonstration and statistical calculations were performed by use of the mean ± the standard deviation of the recorded results in all patients. Differences between the cryoanalgesia and control groups were not significant. Figure 2 shows the postoperative analgesic consumption in both groups. Again there were no significant differences. Figure 3 presents the peak flow measured on the different postoperative days. Here, too, no significant differences were observed between the cryoanalgesia group and the controls.

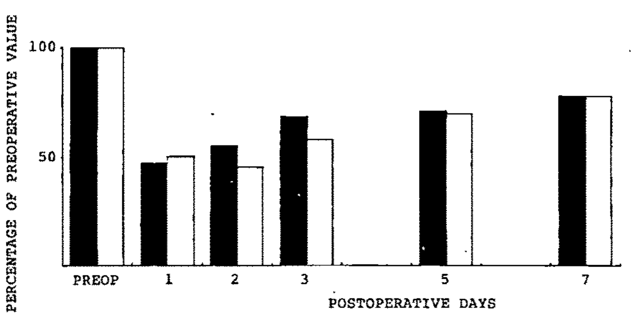

Fig 3. Mean peak expiratory flow as percentage of the preoperative value in the cryoanalgesia (■) and control (□) groups.

Cryoneurolysis was thus not seen to provide any advantage to patients. This is true for the total patient population as well as for the three surgical subgroups.

Neurological examination was performed between postoperative days 4 and 7 and, to the extent that patients were available (21 or 64% of the controls and 22 or 73% of the cryoanalgesia group), 3 and 6 months later. It showed a hypalgesic to anesthetic cutaneous area corresponding in size to the particular dermatomes in the patients who had received cryoanalgesic treatment. In all patients, full sensibility returned after 6 months, although most already had normal neurological findings after 3 months. In the cryoanalgesia group, 6 patients (20%) experienced a marked occurrence of medium to strong neuralgias about 6 weeks after operation, which continued for 2 to 4 weeks and then gradually disappeared.

Comment

Many authors, particularly the advocates of cryoanalgesia, describe lateral thoracotomy as a surgical access entailing severe postoperative pain [7–10, 13]. Our experience, obtained at a surgical clinic performing both abdominal and thoracic surgical procedures, emphatically refutes this. If, when closing the thoracotomy, the adjoining ribs can be sufficiently stabilized against each other (by means of tight pericostal sutures), postoperative pain is far less severe than for a laparotomy of the same scope. This is evidenced in our study by postoperative analgesic consumption. On day 1 after operation, a mean opiate dose of 10 mg (one ampule) sufficed for the patients in the control group. On day 2, consumption dropped to about one third of this (3.4 mg), on day 3 to 2.0 mg, and so on. Nonopiate consumption was also comparatively modest: 380 mg of propyphenazone (about 30 drops or 0.75 ampule of Inalgon) on day 1, 320 mg on day 2, 290 mg on day 3, 160 mg on day 5, and 135 mg (about 12 drops of Inalgon) on day 7 after operation.

Every possible means of optimizing postoperative pain relief appears important, especially when it is a simple-to-use method such as cryoanalgesia. The effectiveness of pain-relieving measures, however, is difficult to ascertain. Because it is impossible to directly measure pain, a scoring system has to be employed. By quantifying pain on a numerical scale, it is made suitable for mathematical comparison. As a matter of course, analgesic consumption plays a complementary role as an objectively measurable dimension. The usefulness of these "measured values," however, is limited because they are not determined solely by the subjective experience of pain intensity but also by emotional and personal factors (eg, one patient might not wish to be considered troublesome whereas another might expect doctors and nursing staff to relieve all discomfort). The mobility score is a similar case. Nevertheless, both methods are indispensable for comparison of analgesically effective measures, and no alternatives are available at present.

The early publications on cryoanalgesia for postthoracotomy pain unanimously reported a significantly lower postoperative analgesic consumption after cryoanalgesia [6–10]. These studies, however, were conducted either with a very small patient population or without examining an untreated control group [9, 13]. Furthermore, they were not able to show that cryoanalgesia was responsible for improved respiratory performance in the early postoperative period compared with a control group [8, 10], as reported by Toledo-Pereyra and DeMeester [14] after bupivacaine blocking of the intercostal nerves. This is despite the fact that the actual advantage of cryoanalgesia compared with systemically administered opiates with their respiratory-depressive effect was considered to be improved ventilation and expectoration.

Doubts as to the effectiveness of cryoneurolysis were voiced by Orr and co-workers [15], who saw no advantage over intravenous administration of morphine using an infusion pump, and recently by Roxburgh and colleagues [16], who, in a strictly conducted double-blind study, found this method to have no particular effectiveness as opposed to conventional pain-relief treatment. These studies fully correlate with the results presented here: the authors were unable to demonstrate the superiority of cryoanalgesia in terms of analgesic consumption, patient mobility (patient sitting up from a lying position without help), and peak expiratory flow.

On the whole, the concept of blocking segmental nerves of the thoracic wall appears to be problematic because, as a result of the sensitive innervation, only the pleura parietalis, intercostal musculature, and pertinent cutaneous areas (which hardly ever represent a particular source of pain) are affected. The sensitivity of the visceral pleura (friction from drainage tubes during respiratory excursions) and of the large thoracic wall muscles, such as the latissimus dorsi and serratus anterior, that are severed in the thoracotomy and are active in every arm movement and every cough, is, however, fully maintained and continues to require systemic pain relief.

Because this study was unable to establish an advantageous effect of cryoanalgesia and because in 20% of the cryoanalgesia patients, severe neuralgiform pain conditions were sometimes observed in the late postoperative phase, a finding also reported by Conacher and co-workers [17] and that caused them to stop routine use of the cryoprobe, we recommend that cryoanalgesia not be used in the future.

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Factors Influencing Long-Term (10-Year to 15-Year) Survival After a Successful Coronary Artery Bypass Operation

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The long-term survival of 6,181 consecutive patients who underwent a coronary bypass operation from 1972 to 1986 was evaluated in relation to certain risk factors: age at the time of operation, sex, preoperative left ventricular function, presence of diffuse coronary artery disease, and previous coronary bypass operation. Advanced age markedly reduced the 10-year and 15-year survival. When compared with the general population, however, the survival of patients in the older age groups (over 60 years) exceeded that of the general population at 10 and 15 years. In patients under 55 years of age, the 10-year and 15-year survival is less than that of the general population. Male and female patients of comparable ages had virtually identical 10-year and 15-year survival rates. Severe left ventricular dysfunction, previous coronary bypass operation, and diffuse coronary artery disease requiring coronary artery endarterectomy all adversely affected the long-term survival rates. Within all age groups studied there was a significant benefit in survival with either one or more mammary artery bypass grafts. The data presented provide an important historical control group that can be used in evaluating the long-term results after successful coronary bypass operations.

(Ann Thorac Surg 1989;48:19–25)

Numerous patient-related risk factors are associated with increased early mortality after coronary artery bypass operations. In our own series of over 7,000 patients followed since 1972, we have consistently identified five variables that significantly increase operative mortality [1, 2]: advanced age, left ventricular dysfunction, previous coronary artery bypass operation, female sex, and "diffuse" coronary artery disease. Associated illnesses such as diabetes mellitus, renal insufficiency, peripheral or extracranial occlusive vascular disease, and chronic obstructive pulmonary disease, as well as the number of diseased coronary arteries and the presence of left main coronary artery stenosis, are all related to increased early mortality in numerous other studies [3–13]. Our data agree with much of this, but we have not been collecting information on many of these variables long enough to define their effect on long-term results. Consequently, this communication will only focus on the 10-year to 15-year results of coronary bypass operation as related to the patients' age at the time of operation, preoperative left ventricular function, sex, the presence of diffuse coronary artery disease, and whether or not previous coronary bypass procedures had been done. In addition, the effects of single or multiple mammary artery bypass grafts will be evaluated.

Patients and Methods

The records of 7,211 consecutive patients who underwent coronary bypass operations from August 1, 1972, through June 30, 1986, were reviewed. For the purpose of this study 450 patients who died within 90 days of operation were considered operative deaths and were excluded. One hundred fifty-three patients with combined valve replacement and coronary artery bypass grafting have been previously reported [1] and were also excluded from this analysis. Finally, 17 patients with unknown birth dates and 410 foreign patients were excluded, leaving a study group of 6,181 patients, 5,189 men and 992 women. Follow-up was obtained through a mail and telephone survey, in addition to a review of the United States National Death Index,* and is available for virtually all patients.

The patients were divided into seven subgroups based on their age at the time of operation: group A, 593 patients, less than 45 years; group B, 748 patients, 45 to 50 years; group C, 1,117 patients, 50 to 55 years; group D, 1,362 patients, 55 to 60 years; group E, 1,154 patients, 60 to 65 years; group F, 778 patients, 65 to 70 years; and group G, 429 patients, more than 70 years.

Our definition of diffuse coronary artery disease, as well as the indication for coronary artery endarterectomy and the techniques employed, have been reported [2, 14]. Data were analyzed by the χ^2 test and the methods of Cutler and Ederer [15]. Life tables for the United States population were obtained from the United States Public Health Service [16].

Determinations of left ventricular ejection fraction were

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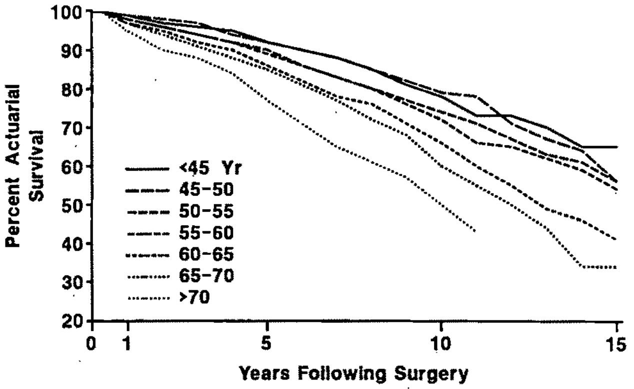

Fig 1. Effect of patient's age on long-term survival for all 6,181 patients in the study. For standard errors, see Table 1.

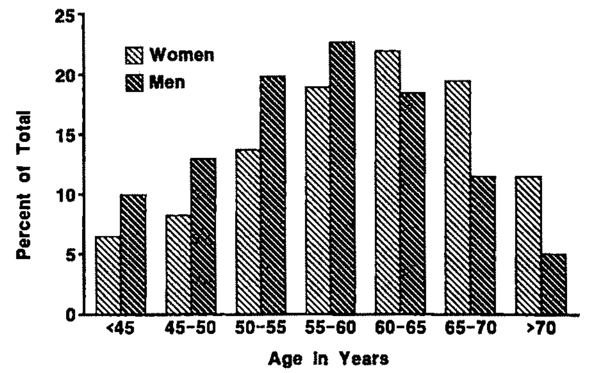

Fig 2. Distribution of age groups and sex for all 6,181 patients in the study.

not available for many patients operated on early in the series. Therefore severe left ventricular dysfunction is defined as two or more akinetic wall segments or a left ventricular ejection fraction less than 0.40. If there is global hypokinesis or the left ventricular ejection fraction is less than 0.20 we assign a double risk factor.

Results

Age and Sex

Age at the time of operation has a profound effect on late survival (Fig 1; Table 1). Ten-year actuarial survival decreased from 78.3% (standard error [SE], 2.2%) in patients under 45 years of age to 60.4% (SE, 2.6%) in patients aged 65 to 70 years. Similarly, the 15-year survival decreased from 64.6% (SE, 4.9%) in patients under 45 years of age to 35.0% (SE, 6.6%) in patients aged 65 to 70 years. Because of these dramatic differences, it is imperative to look at the proportion of patients in various age groups whenever a specific risk factor is evaluated.

In evaluating the effect of sex on long-term survival, it was noted that females had a much higher representation in older age groups (Fig 2). However, when we compared sexes in comparable age groupings, survival was virtually identical (Fig 3).

Comparison With the United States Population

When the survival of our patients was compared with that of age- and sex-matched groups in the general population, some very interesting facts were observed. The thrust of this analysis was to compare survival during the first 5 years after operation with the second 5 years in the same patients. Therefore, we considered only patients operated on more than 5 years ago. In addition, patients with severe left ventricular dysfunction, repeat operation, multiple coronary artery endarterectomies, or female sex were excluded, leaving a cohort of 2,605 men with no additional risk factors; a group that should theoretically have the best long-term results. In the age groups under 55 years, the 5-year survival approximates that of the general population. There is a marked acceleration in annual mortality, however, in the second and third 5-year periods after operation. In the older age groups (over 60 years) the survival of the surgical patients exceeds that of the general population throughout the period observed (Fig 4).

Left Ventricular Function and Repeat Bypass Operation

Except for age, left ventricular dysfunction at the time of coronary bypass operation is the dominant factor affecting long-term survival. All age groups are equally distributed among the classifications of ventricular function ($p = 0.7$). Patients undergoing repeat bypass operation and patients requiring multiple coronary artery endarterectomies were excluded from this analysis. The results, summarized in

Table 1. Standard Errors for Figure 1[a]

Age Range (yr)	Follow-up (yr) 5	10	15
Under 45	1.2	2.2	3.9
45–50	1.0	1.8	5.3
50–55	0.9	1.6	4.2
55–60	0.9	1.5	3.6
60–65	1.1	1.8	4.7
65–70	1.4	2.6	6.6
Over 70	2.2	4.5	NA

[a] All numbers are given as percentages.

NA = not available.

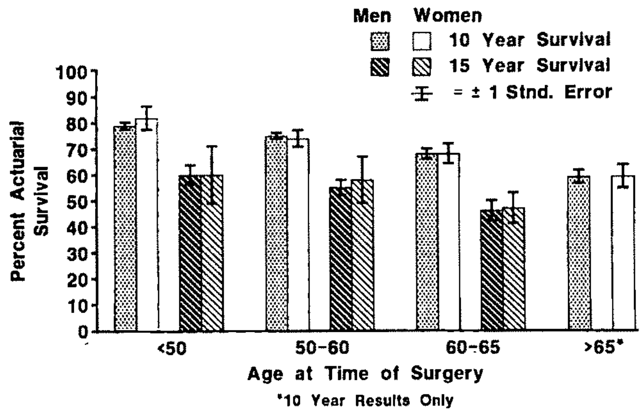

Fig 3. Sex, age, and long-term survival for all 6,181 patients in the study.

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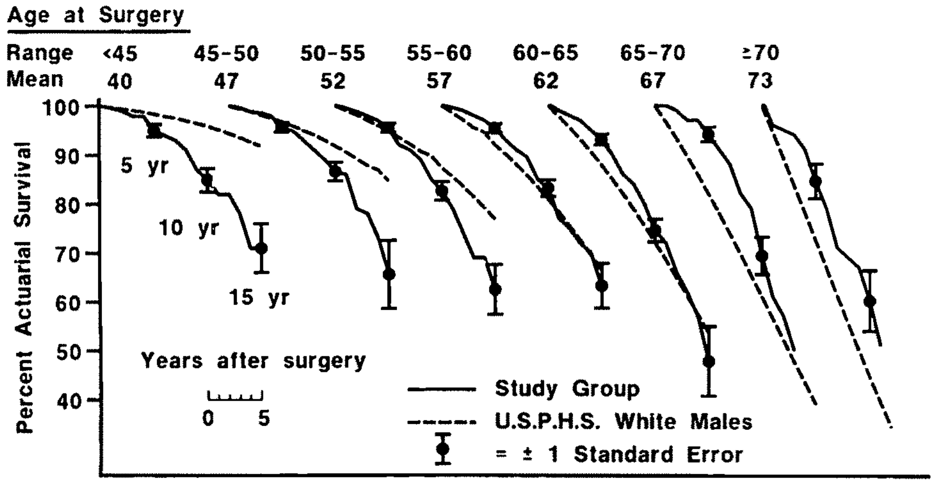

Fig 4. Actuarial survival for male patients with no risk factors by age versus United States Public Health Service white males; 2,605 patients: male, no risk factors (severe ventricular dysfunction, repeat operation, two or more coronary endarterectomies), operated on before 1983.

Figure 5, are dramatic. Ten-year survival is reduced from 79.1% (SE, 0.8%) in patients with normal or near-normal left ventricular function to 49.0% (SE, 2.1%) in patients with severe left ventricular dysfunction, to 35.1% (SE, 5.5%) in patients with global dysfunction.

Figure 6 summarizes the comparison between patients having their primary coronary bypass operation and patients having a repeat operation. Patients with severe left ventricular dysfunction or multiple coronary artery endarterectomies were excluded. The remaining group was homogeneous in age distribution ($p = 0.75$). Clearly there is a marked disparity in survival after 5 years, with a substantial increase in the annual mortality of the group having repeat operation.

Diffuse Coronary Artery Disease

Figure 7 summarizes the comparison between those patients with conventional grafts only, those requiring one coronary endarterectomy, and those requiring multiple coronary artery endarterectomies. Patients with severe left ventricular dysfunction and those having repeat coronary bypass operations were excluded. As there was a statistically significant age disproportion in the older age groups (over 65 years) ($p < 0.001$), with more elderly patients requiring single or multiple coronary artery endarterectomies, only patients under 65 years were considered. This group was homogeneous in age distribution ($p = 0.7$). Furthermore, as we have only compiled endarterectomy data since 1978, there is no survival data beyond 10 years for these patients. Up until 10 years, however, there is only a slightly decreased long-term survival in patients with one or more coronary artery endarterectomies compared with those patients with conventional grafts only. In addition, there was no statistically significant difference when patients requiring a single right coronary artery endarterectomy were compared with those requiring a single left coronary artery endarterectomy [2].

Mammary Artery Bypass Grafts

When analyzing the effects of mammary artery bypass grafts on long-term survival, the age distribution of patients was not homogeneous ($p < 0.001$). As expected, a higher percentage of young patients received one or two mammary artery bypass grafts. The patients were therefore divided into three groups: under 50 years, 50 to 60 years, and 60 to 70 years. Patients with severe left ventricular dysfunction and those undergoing repeat bypass operation or multiple coronary artery endarterectomies were excluded. Within each age group there was a signif-

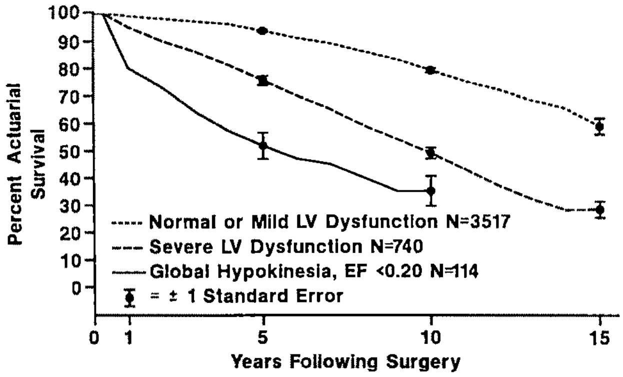

Fig 5. Effects of left ventricular (LV) function on survival for 4,371 patients; multiple endarterectomy and repeat bypass operation excluded.

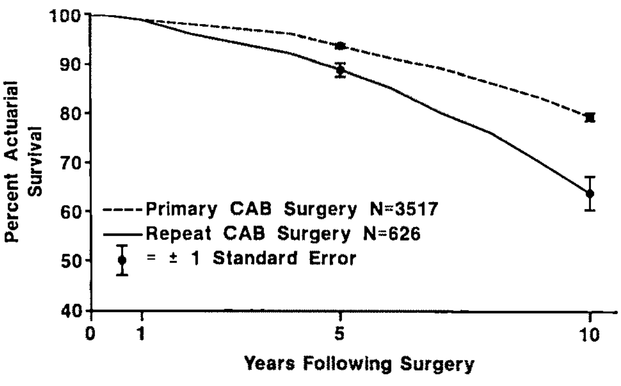

Fig 6. Comparison of primary versus repeat coronary artery bypass (CAB) operation for 4,143 patients with no other risk factors.

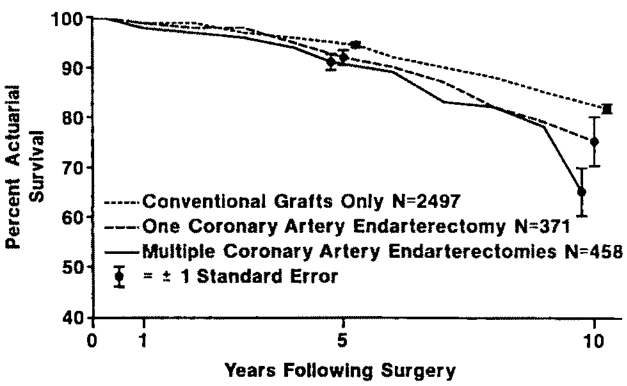

Fig 7. Survival in patients with diffuse coronary artery disease requiring two or more coronary endarterectomies for 3,326 patients under age 65 years with no other risk factors.

icant benefit in survival with either one or more mammary artery bypass grafts, although there did not appear to be any increased benefit with multiple mammary artery grafts. Not surprisingly, this benefit became more obvious the longer the patients were followed (Fig 8). A complete analysis of the long-term results of mammary artery grafts is currently underway and is beyond the scope of this paper, but there does not appear to be any increased benefit when the mammary artery is used to bypass the left anterior descending coronary artery (598 patients: 10-year survival, 83.5%; SE, 1.7%; 15-year survival, 62.2%; SE, 5.7%) rather than a diagonal or circumflex marginal branch (846 patients: 10-year survival, 82.1%; SE, 1.5%; 15-year survival, 63.6%; SE, 4.3%).

Comment

A number of studies have been published that describe the long-term (over 10 years) results after a coronary bypass operation [3, 5, 8, 9, 12]. Certainly there is an ongoing need to precisely evaluate survival in the various subgroups of patients that undergo coronary bypass operations; it is important information that can be used to compare the durability of different modes of treatment. In addition, it supplies valuable predictive knowledge to the patients, their families, and referring physicians.

For the purpose of this communication, all patients who died within 90 days of coronary bypass operation were considered operative deaths. Although surgical mortality is usually limited to 30 days, modern therapies can often support patients with multiple complications for far longer than that before they die; therefore only patients who survived 90 days were defined as having had a "successful" operation. As all of the risk factors we looked at markedly increased operative mortality, by only looking at the long-term results of 90-day survivors, we have virtually eliminated the effects of operative fatalities on long-term survival curves. Equally important, it must be emphasized that the cumulative effects of operative and long-term deaths are additive for an individual or group of patients. The purpose of this paper, however, is only to look at the effects of preoperative risk factors on the long-term survival after a successful operation.

We have previously reported our 30-day mortality results [2], which ranged from 0.5% in 1,134 low-risk patients to over 25% in 197 patients with multiple preoperative risk factors combined with diffuse coronary artery disease requiring multiple coronary artery endarterectomies. The risk factors we analyzed in relation to early mortality were the same ones that we considered in this paper: age, left ventricular dysfunction, repeat bypass operation, female sex, and diffuse coronary disease requiring coronary artery endarterectomy. Insulin-dependent diabetes mellitus is an additional well-documented risk factor that increased early mortality in our surgical series; we do not have enough long-term data to analyze the 10-year to 15-year effects, although our intermediate results have been published [17].

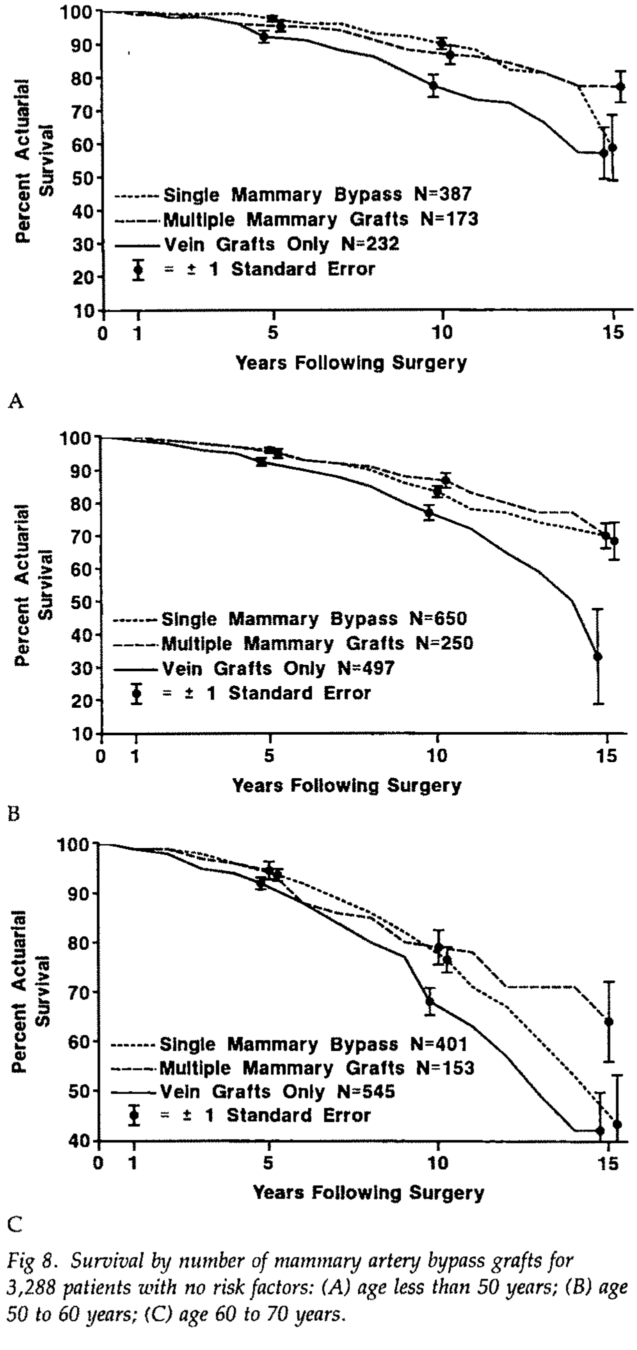

Fig 8. Survival by number of mammary artery bypass grafts for 3,288 patients with no risk factors: (A) age less than 50 years; (B) age 50 to 60 years; (C) age 60 to 70 years.

A patient's age at the time of coronary bypass operation is one of the most significant predictors of early mortality [2, 6, 10, 13, 14]. Not unexpectedly, this is also true for late mortality in the series presented here (see Figs 1, 4) as well as others [5, 9]. What was surprising was the markedly increased mortality in the second and third 5-year periods after operation that were observed in the younger age groups (under 55 years). In the older age groups (over 60 years) the survival after coronary bypass operation exceeded that of the general population throughout the period of observation. This is almost identical to the findings of Cosgrove and associates [9] in their 10-year results after primary myocardial revascularization.

Of additional importance is the fact that, in the youngest groups, most of the patients had mammary artery bypass grafts (under 45 years: 194/262 patients, 74%; 45 to 50 years: 278/359 patients, 77.4%). Also, all of the operations were primary in patients with good left ventricular function and without diffuse coronary artery disease. The addition of any risk factor or multiple risk factors, or the failure to use mammary artery grafts, would make the disparity between the surgical group and the general population even greater. As our operative mortality for this type of patient is only 0.5% [2], the attrition curves for the patient group, early and late mortality combined, would be virtually identical to those seen in Fig 4.

Female sex is another well-accepted predictor of increased early mortality after coronary bypass operations [1, 6, 10]. In our series, as well as others [12, 13], there is a much higher proportion of women patients in the older age groups (see Fig 2), almost certainly because of the protective effects of estrogen in premenopausal women. Richardson and Cyrus [13] found a significantly lower ($p < 0.001$) 5-year survival in women. Killen and coworkers [12] found that the absolute survival of female patients in their series was as good as that observed in men; the female patients, however, did not achieve the expected survival pattern of a matched general population that was observed in their male patients. Whereas the absolute survival of women in our series was not as good as that of men, the 10-year and 15-year survival in equivalent age groups was virtually identical (see Fig 3). As the survival of women in the general population is better than men of the same age, there is still an increased risk of late death in female patients, although it is not as great as we had expected.

Left ventricular dysfunction profoundly affects operative [1, 2, 6, 7, 10] and late mortality [3, 8, 9, 11, 13]. It is commonly the most significant predictor of both early and late death [5]. Our own results (see Fig 5) are so clear-cut that little discussion is required. The 15-year survival decreases from 59% in patients with normal or near-normal left ventricular function to 28% in patients with severe left ventricular dysfunction. The desirability of doing an operation—when indicated—before serious injury to the left ventricle occurs is obvious. Severe left ventricular dysfunction is not a contraindication to coronary bypass operation, as the long-term survival of many of these patients is abysmal when treated medically; it does, however, substantially increase the operative risk and reduce long-term survival.

The operative risk of a patient having a repeat bypass procedure is at least two to three times the risk of a first operation in a similar patient [18–20]. In addition, Rutherford and colleagues [11] found that a prior cardiac operation is a significant predictor of late death ($p < 0.01$) when compared with primary operations. Even eliminating the increased operative risk by only considering 90-day survivors, we found a significant and persistently increased late mortality in our patients undergoing repeat operations (see Fig 6). There is no clear explanation for this, but it is probably due in part to the more diffuse nature of the coronary artery disease seen in patients having repeat operations, and the decreased capability to completely revascularize many of these patients [20].

We have recently described our entire experience with coronary artery endarterectomy in the treatment of diffuse coronary artery disease [2, 14]. Operative mortality is increased in the presence of diffuse coronary artery disease, whether or not endarterectomy is performed [2, 10]; it is even higher in patients requiring multiple endarterectomies. The long-term survival of these patients, as summarized in Figure 7, was therefore better than we had expected, and is further testament to the durability of the techniques we use. The clinical status of the patients and graft patency data have been published [2, 14].

Finally, the data presented in Figure 8 confirm the significant and persistent value of mammary artery bypass grafts in improving long-term survival in all age groups up to 70 years old, for periods up to 13 years after operation. The work done at the Cleveland Clinic has proved, virtually beyond doubt, the durability of mammary artery bypass grafts and their beneficial effect [9, 21]. Although we have not yet completed a comprehensive study of our patients with mammary artery grafts, two interesting trends are apparent. First, there does not seem to be any additional benefit to multiple mammary artery grafts compared with single mammary artery grafts. Also, there seems to be no difference in the long-term results when a single mammary artery graft was done to the left anterior descending coronary artery (598 patients; 10-year survival, 83.5%; SE, 1.7%; 15-year survival, 62.2%; SE, 5.7%) rather than a diagonal or circumflex marginal branch (846 patients; 10-year survival, 82.1%; SE, 1.5%; 15-year survival, 63.6%; SE, 4.3%). We cannot explain this as yet, but only point it out, as the beneficial effects described by Loop and associates [21] related only to patients with mammary artery grafts to the left anterior descending coronary artery.

Possible reasons for these curious observations have to do with our philosophy regarding mammary artery bypass grafts. We routinely use the mammary artery to bypass the most critically obstructed left-sided coronary artery; it is not used in diffusely diseased coronary arteries where endarterectomy is required, nor routinely in vessels less than 1.5 mm in size. Thus a mammary artery is almost always placed into a relatively normal distal coronary artery of large diameter that has a critical proximal obstruction, and that appears to be the most important vessel for a particular patient, whether that is the left anterior descending or a large diagonal or circumflex branch. Having bypassed the most seemingly important vessel with a mammary artery, combined with the expected long-term patency of over 90% and the excellent long-term survival of these patients, it will probably take substantially larger numbers of patients followed for longer periods of time to demonstrate the expected additional benefit that would be gained by a second mammary artery bypass graft to a less important coronary artery.

The data presented here on the long-term survival of patients having a coronary bypass operation and various risk factors that affect that survival provide information on the durability of an important mode of therapy for patients with severe coronary artery disease. There are a number of invasive procedures being developed for patients in whom medical treatment is not indicated. Our work, and that of several other groups, establishes a historical control group that can be used to evaluate the relative merits of other invasive or noninvasive treatments, both short-term and long-term. Perhaps more important, it is obvious from the data presented that any meaningful discussion of long-term results must take into account the preoperative condition of the patient under consideration, particularly age and ventricular function.

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DISCUSSION

DR H. NEWLAND OLDHAM, Jr (Durham, NC): I enjoyed reading the manuscript that was provided by Dr Brenowitz. This report of the long-term results in 6,000 operative patients by the Milwaukee group clearly describes the factors influencing 10-year and 15-year survival after a coronary bypass operation.

The Duke Coronary Artery Data Bank contains approximately 8,000 surgical patients, and also has a roughly equivalent group of medical patients. An adjusted Cox model comparison of survival out to 12 years shows a significant increase in long-term survival after surgical treatment in the overall population after adjusting for baseline inequalities. Three major factors are associated with the significant long-term survival improvement with operation. These are the extent of coronary artery disease, poor medical prognosis due to factors such as age or ventricular dysfunction, and a more recent operative date. This improvement in surgical over medical survival is consistent comparing 1970, 1977, and 1984 even though in each successive time period higher-risk patients were accepted for operation.

The improvement is quite dramatic in patients with reduced ventricular function. Thus, the larger the medical risk the greater the benefit from operation; or, said another way, the sicker the patient the greater the benefit.

This increase in surgical survival has progressed so that by 1984, almost all subgroups have shown an improvement. Expressed as a hazard ratio, by 1984 the 95% confidence limits demonstrate benefit in all groups except single-vessel disease.

It is important to stress that the subgroups of patients with reduced long-term surgical survival are not bad surgical patients.

These are the same patients who, if treated medically, will have an even worse prognosis. Thus, selection of only low-risk patients deprives patients who would achieve the greatest survival benefit from operation.

In this context I wonder if Dr Brenowitz would expand his thoughts on the use of internal mammary artery bypass grafts. I was interested to note that single or double mammary artery grafts equally improved survival and that use of an internal mammary artery graft to virtually any coronary artery seemed to provide the same long-term survival benefit.

DR BRENOWITZ: The answer is I don't know. We're going to look at that more carefully. These are raw data; it's very surprising. I think that it is clear that in every age group that we studied, from the youngest to the oldest patients, the presence of a mammary artery graft increased survival throughout the entire period of observation, up to 15 years, and the difference between patients receiving mammary artery grafts and patients receiving only vein grafts was more dramatic the longer the follow-up. We have not looked at it carefully enough to know the effect of left ventricular function on those groups, how many of the patients had endarterectomies, or how many patients had redo operations, and I think some of these other factors might play a role.

I personally think that if the patient has a large lateral marginal branch or a very large diagonal branch, that is probably a much better artery to put the mammary artery into than a diffusely diseased and small left anterior descending coronary artery. Dr Johnson has been doing that for quite some time. So we tend to put the mammary artery, when we use a single left or right mammary artery, into the best artery available and not necessarily just into the anterior descending. Why two or three mammary bypass grafts don't seem to do better than one I cannot explain.

I would like to say two things in closing. First, we hear a lot about angioplasty and other methods of treatment, and people are talking about what they call long-term results. I think Dr Akins was more precise when he talked about intermediate-term results. Certainly 10-year and now 15-year results are available for bypass grafting. Furthermore, it is clear from our data that as time goes on the results seem to deteriorate, although not as much if you use mammary artery bypass grafts. I think that this is important information that can be used to compare the durability of various treatments.

And finally, even in the best groups of patients it is obvious that after 5 or 6 years the annual mortality rate increases significantly. Clearly other things are required to try to improve the survival in these patients, such as risk factor modification, diet, exercise, and cessation of smoking.

Freehand Homograft Aortic Valve Replacement—The Learning Curve: A Technical Analysis of the First 31 Patients

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Division of Cardiothoracic Surgery, Emory University School of Medicine, Atlanta, Georgia

The technique for implanting the homograft aortic valve is significantly more complex than that of either the bioprosthetic or mechanical valve. During development of the procedure, errors of technique were committed; a critical analysis of the learning experience is presented. In the initial 31 patients, the following problems were encountered: mitral stenosis secondary to inadequate debulking of the homograft (1 patient), prolapse of a single homograft leaflet necessitating valve replacement three days later (1 patient), incorrect homograft orientation with torsion in a calcified aorta necessitating subsequent replacement (1 patient), and aortic sinus perforation (thawing injury) (1 patient). In addition, another 4 patients had diastolic murmurs thought to be secondary to inadequate tension setting of the homograft commissural posts. From this experience, several important technical considerations for homograft replacement of the aortic valve were noted: use of interrupted subannular sutures; careful inspection for aortic perforation (thawing); extensive trimming of the homograft septum and mitral remnant; orientation of the homograft to the recipient aorta to obtain the best commissural and sinus alignment; selection of another type of valve if the size of the recipient annulus is greater than 27 mm; retention of the homograft sinus, which orients to the recipient noncoronary sinus (for a calcified aorta); and exaggerated tension on the homograft commissural posts before initiation of the second suture line. There has been 1 hospital death and no late deaths. Adherence to rigid principles of technique has resulted in no further valve replacements and no incidences of valvular leakage at early or late follow-up.

(Ann Thorac Surg 1989;48:26–32)

Interest in use of the homograft valve for aortic valve replacement was initiated in the early 1960s by Ross [1] and Barratt-Boyes [2]. Since that time, several experienced surgeons [3–8] have advocated use of this valve as an equal, if not superior, choice for aortic valve replacement in young and older patients alike. To achieve clinical success, however, it is noteworthy that these same surgeons have spent considerable time in the development of a technique that assures excellent immediate and intermediate-term results [4–9]. Although excellent results have been achieved and reported by these surgeons, a precise outline of implantation technique has been infrequently available [10].

Careful processing and storage of the cryopreserved homograft valve has now made it immediately available to large numbers of surgeons, but past successful methods of implantation have been related more to technical artistry and experience than to specific step-by-step instruction. Without specific tutorial guidance from those having years of experience with freehand implantation techniques, potential problems can occur immediately or shortly after implantation; these necessarily dampen enthusiasm for what may prove to be an important and superior alternative for aortic valve replacement.

The purpose of this report is to present a detailed technical analysis of my initial experience using the cryopreserved homograft valve in the aortic position with special emphasis on difficulties encountered during the learning curve for freehand implantation.

Material and Methods

Over the past 18 months, 31 cryopreserved homograft aortic valves (CryoLife Laboratories, Marietta, GA) have been implanted freehand by me at Emory University Hospital. There were 22 male and 9 female patients with a mean age of 50 years. The range of valve sizes is shown in Table 1. Aortic valve replacement was performed for aortic stenosis in 14 patients, aortic regurgitation in 11 patients, and combined aortic stenosis and aortic regurgitation in 6 patients. Two patients had prior coronary artery bypass grafting and 1 patient, a previous porcine bioprosthetic aortic valve replacement. Freehand homograft aortic valve replacement was performed with coronary artery bypass grafting in 3 of the patients and for healed endocarditis in 3 patients. In 2 patients, aortic root enlargement through the noncoronary sinus was combined with homograft valve replacement.

Technique of Operation

Because of the increased time required to perform the operation, superior myocardial preservation becomes extremely important. To accomplish these goals, bicaval

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Table 1. Distribution of Valve Sizes in 31 Patients

Valve Size (mm)	No. of Patients
17[a]	3
18	2
19	2
20	4
21	4
22	8
23	5
24	1
25	1
26	1

[a] Two patients had noncoronary sinus root enlargement with glutaraldehyde-treated pericardium.

cannulation, systemic hypothermia to 21° to 25°C, and frequent administration of 4°C crystalloid cardioplegia are used.

A standard "hockey-stick" aortotomy incision into the noncoronary sinus with removal of all annular and subannular calcium is performed. The aortic incision is planned to avoid any area of the aorta where commissural sutures will be placed. The diameter of the aortic annulus and the transcommissural diameters are measured to a tight fit with a disc sizer, and a homograft 3.0 mm smaller than the diameter of the annulus is thawed while interrupted pledgeted 3-0 sutures are inserted. These sutures are placed approximately 3.0 mm below the native annulus but in such a manner as to avoid the conduction system and the body of the anterior mitral valve leaflet. At these two levels, the sutures are moved back to the level of the native annulus. The subannular sutures are also placed low enough to avoid encroachment on the coronary ostia (Fig 1). I and others [4, 6, 10] believe that interrupted sutures for the proximal row allow better exposure and less chance for homograft malrotation than the continuous suture technique.

Preparation of Homograft

Once thawed, the homograft should be carefully inspected under magnification for intimal and medial tears that may become manifest at the time of warming. Any abnormality of the sinuses must also be noted, with particular attention paid to potential cusp prolapse. Next, the anterior mitral leaflet and then the septum of the homograft are carefully trimmed to a perfect cylinder 3 to 4 mm in width (Fig 2). The homograft septum is debulked thoroughly and the homograft aorta divided distally 1 cm above the commissural attachments.

Only two of the three homograft sinuses are scalloped approximately 3 mm above the annulus in a U, not V, shape. This scalloping can be more precisely performed prior to insertion of the homograft into the aortic root, where manipulation and visibility are more limited. The sinus oriented to the recipient noncoronary sinus is not scalloped; this is particularly helpful when aortic wall calcification is dense at the lower portion of the sinus or when it is desirable to use the homograft noncoronary sinus wall to conform symmetrically to the recipient aorta, thereby maintaining the cylindrical configuration of the entire homograft unit. The latter technique is useful when the recipient noncoronary sinus is thinned and degenerative and in need of reinforcement. As a useful general guide, the depth of the scallop will be determined by the distance between the coronary ostia and the proximal suture line.

Orientation of Homograft

Although orientation of the anterior mitral leaflet of the homograft to the recipient septum gives the most even distribution of bulk within the annulus, the most versatile approach is to orient the homograft to whatever position gives the best commissural alignment. Orientation of the homograft mitral remnant to the left main coronary artery minimizes any bulky septal impingement on the ostium. If the transcommissural diameter (at the sinotubular ridge) is slightly smaller than the homograft aortic wall, orientation of the largest homograft sinus toward the recipient left sinus (which is usually long) allows any excessive circumference of the homograft aortic wall to be distributed evenly on either side of the left main coronary artery and into the noncoronary sinus. Although these guidelines are potentially helpful and should be appreciated, the most frequent practice has been to orient the homograft in the most natural position, ie, left sinus of the homograft to the left sinus of the recipient.

Once oriented, the homograft is inverted (by pushing the commissural posts centrally) so that the leaflets occupy an external position (Fig 3). This maneuver is performed to enhance visibility when passing the subannular 3-0 sutures into the muscular and fibrous base of the homograft valve. The homograft is lowered into position, but before the individual sutures are tied, the commis-

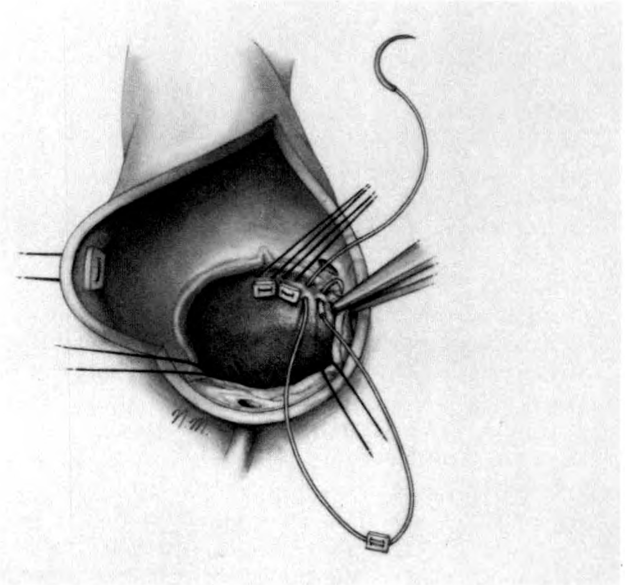

Fig 1. Placement of subannular sutures below plane of left and right coronary ostia.

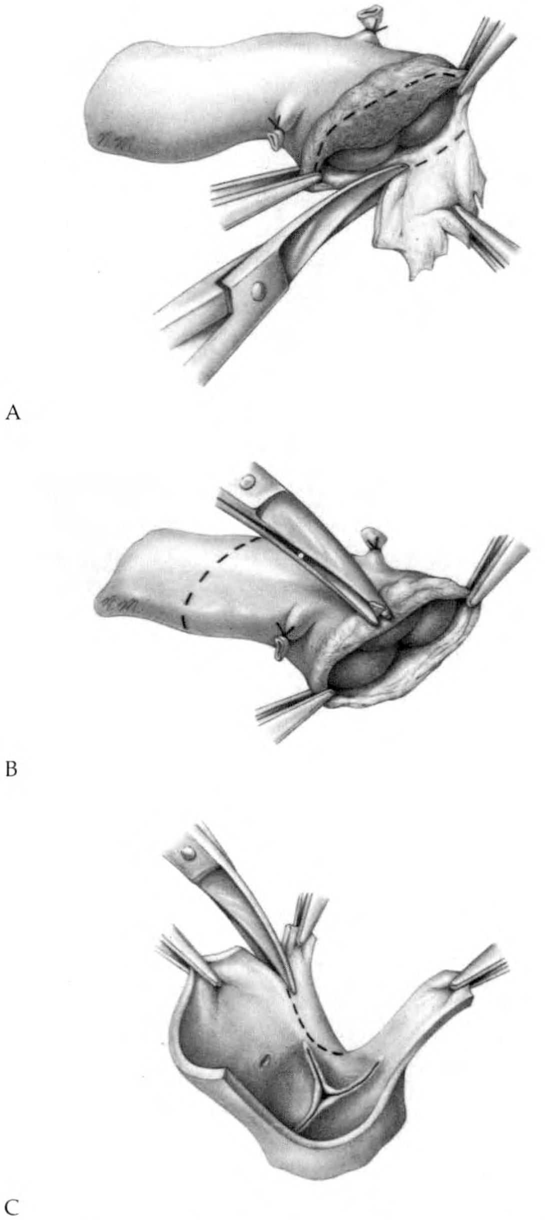

Fig 2. (A) Trimming anterior leaflet of the mitral valve and septum 3 to 4 mm below the homograft leaflets. (B) Debulking the septal muscle remnant. (C) U-shaped scallop of left and right sinuses only; thus retaining aortic wall, which orients to recipient noncoronary sinus.

sural posts are temporarily everted to check for suture entrapment. Once the sutures are tied, the valve is everted from the ventricle (Fig 4), and tension is set on the commissural posts, thus elevating the homograft commissures to a plane approximately 5 mm above the top of the native commissural attachments (Fig 5). This latter maneuver avoids leaflet prolapse under diastolic pressure once the operation has been completed. The direction of force applied to the commissural posts is that of the native commissures. A second row of sutures (4-0 Prolene, RB-1; Ethicon, Inc, Division of Johnson & Johnson, Somerville, NJ) evenly distributes the homograft throughout the circumference of the aorta.

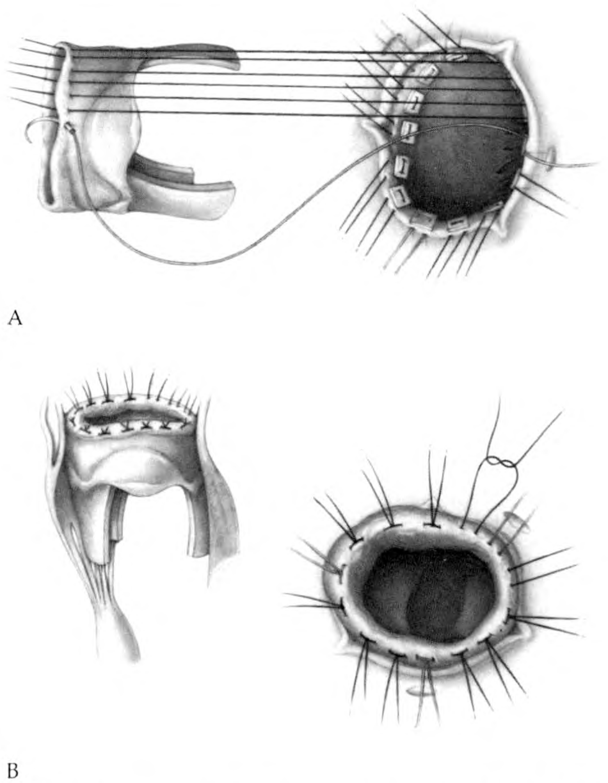

Fig 3. (A) Inversion of homograft so that leaflets are external and readily visible. (B) Homograft as it appears in left ventricular cavity as sutures are tied.

Anatomical Variations

When there is a marked discrepancy between the aortic annulus diameter (small) and the body surface area of the patient (large), and aortic annulus enlargement is indicated, the homograft can still be used with a modification of the technique of Manouguian and Seybold-Epting [11]. The aortotomy incision is carried down into the anterior leaflet of the mitral valve, and a generous portion of glutaraldehyde-treated pericardium is used to expand the native annulus to the desired homograft size (Fig 6). The annulus is sized, canting the disc sizer into the patch and

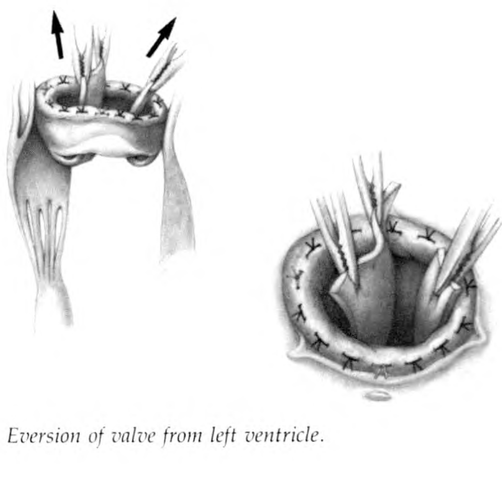

Fig 4. Eversion of valve from left ventricle.

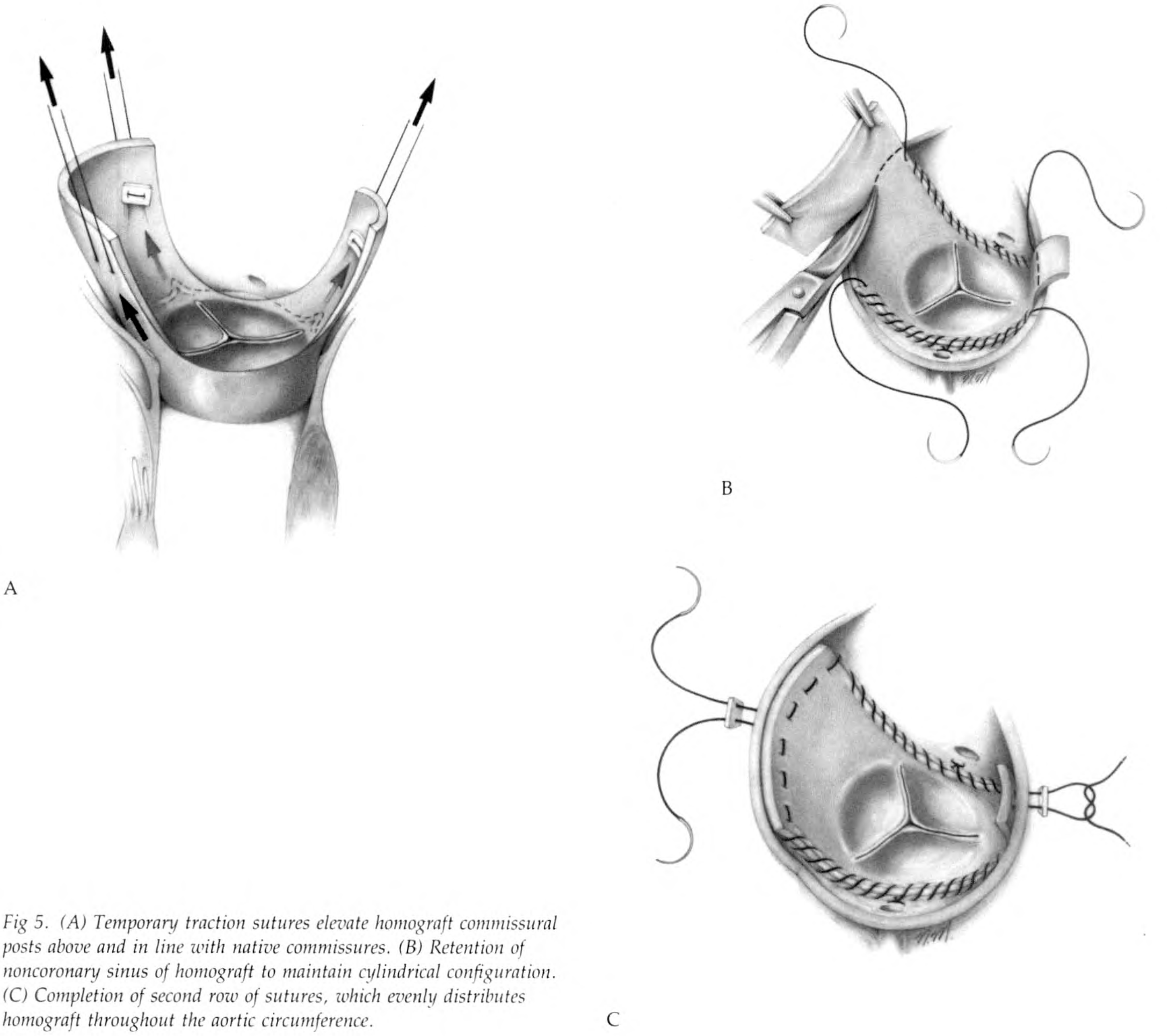

Fig 5. (A) Temporary traction sutures elevate homograft commissural posts above and in line with native commissures. (B) Retention of noncoronary sinus of homograft to maintain cylindrical configuration. (C) Completion of second row of sutures, which evenly distributes homograft throughout the aortic circumference.

marking the "new, expanded" pericardium with an ink pen. The interrupted 3-0 sutures are then passed through the pericardium at this level, and the suture line is completed in both the native and expanded pericardial annulus (Fig 7). The homograft valve is then inserted as described previously (Fig 8).

Results

There has been 1 death among the 31 patients for a combined early and late mortality of 3.2%. The patient died on the seventh postoperative day of an arrhythmia thought not to be related to the homograft valve. The patient was to be discharged from the hospital the following day.

Explantation of the homograft was necessary in 5 patients, in 2 immediately and in 3 at 3, 8, and 37 days after implantation. In the 2 patients requiring immediate explantation, the reason was impairment of mitral valve function (restriction of anterior leaflet motion with left atrial pressure changes of mitral stenosis) in 1 patient and unacceptable aortic insufficiency after implantation of a 26-mm homograft into an aortic annulus 29-mm in diameter in the other.

In 1 patient, a 23-mm homograft valve was explanted four days after implantation. The valve was preserved on removal and subsequently demonstrated prolapse of the noncoronary cusp when tested under hydrostatic pressure. Another patient required replacement of the homograft with a mechanical valve eight days after implantation. The 25-mm homograft demonstrated perfect apposition of the leaflets when the valve was viewed in the collapsed state, but was clearly leaking under diastolic pressure. The original reason for insertion of the homograft was to replace a failed 29-mm porcine bioprosthesis. In the final patient who required removal of the homograft (at 37 days), partial dehiscence of the valve, which was implanted into a heavily calcified aorta and annulus, developed. Torsion from malalignment of the homograft was also thought to be responsible.

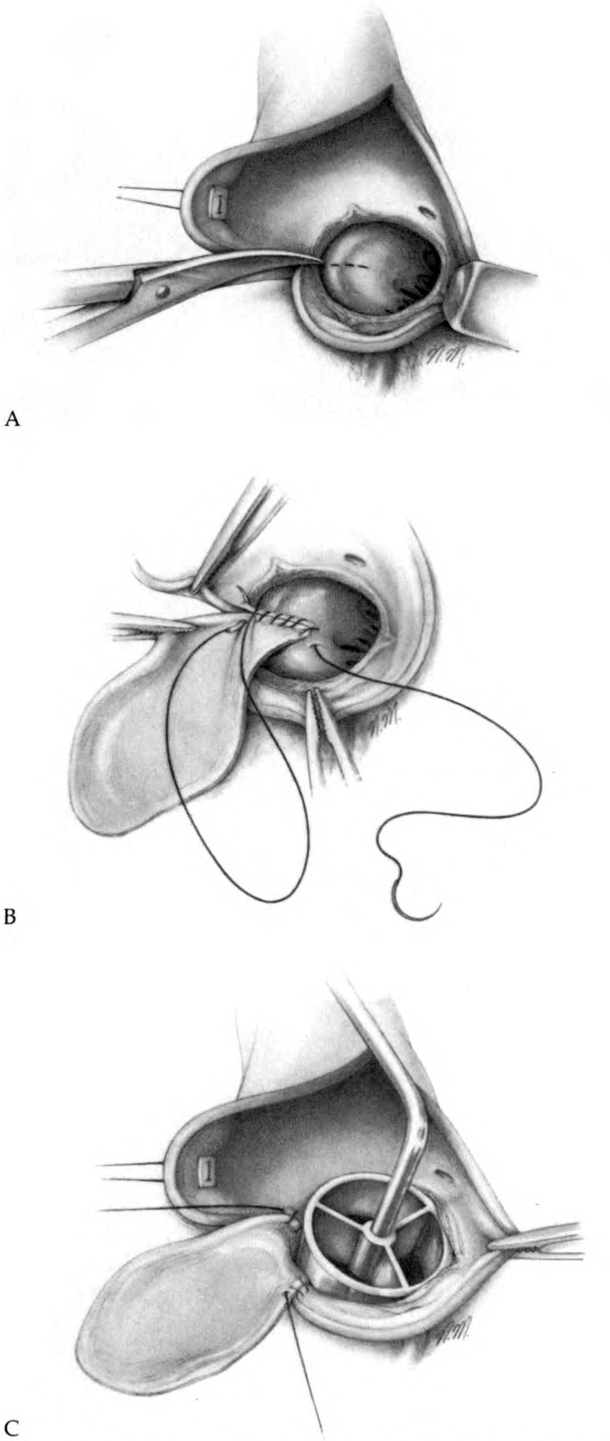

Fig 6. Technique employed for expanding aortic root diameter using pericardial gusset when annulus is hypoplastic. See text for details.

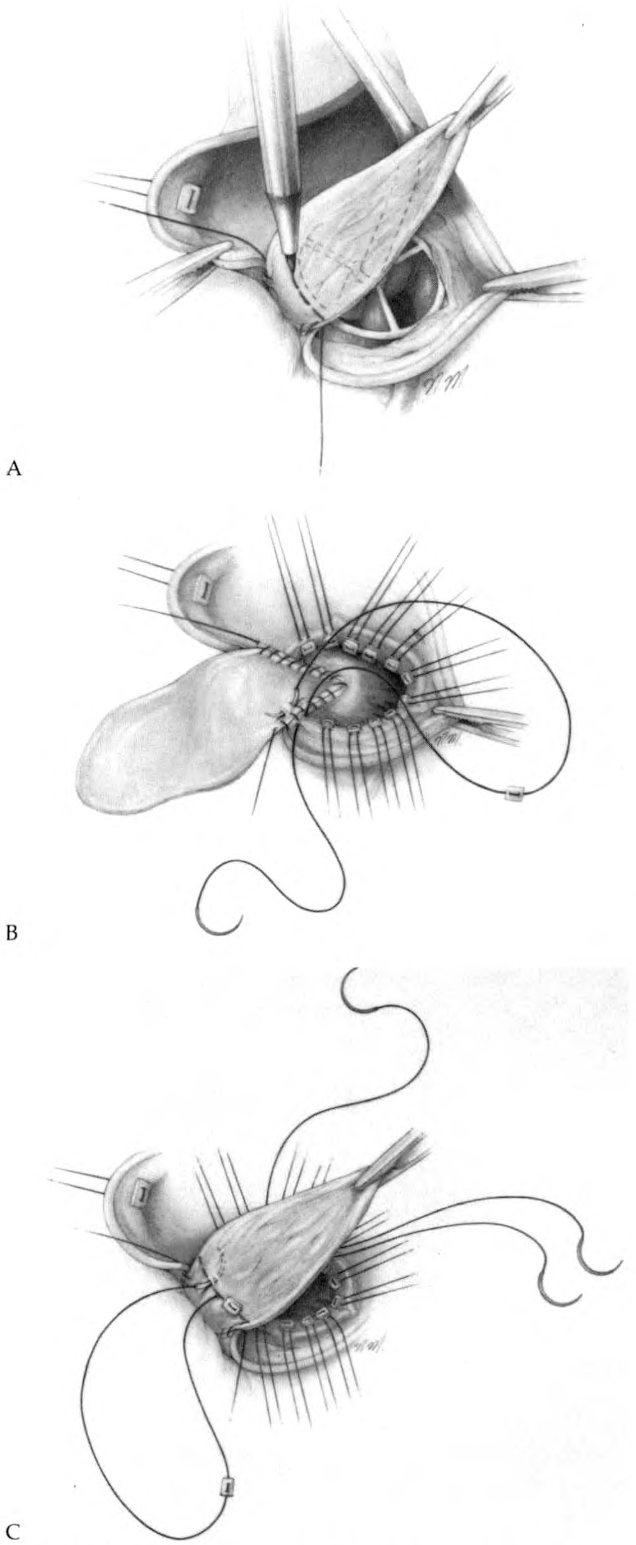

Fig 7. Determining new plane of valve and placement of sutures when aortic annulus is enlarged into noncoronary sinus and anterior leaflet of mitral valve.

Comment

Freehand aortic homograft implantation in the subcoronary position was introduced by Ross [1] in 1962 and used subsequently by Barratt-Boyes [2] in 1964. Experience was limited to very few centers because of complex problems with availability, procurement, and preservation, difficulty of insertion, reports of early failures, and availability of satisfactory alternative bioprostheses [6, 8, 12–15].

Recent interest in freehand homograft replacement of the aortic valve has been generated by several factors: the suggestion that cryopreserved valves contain living cells

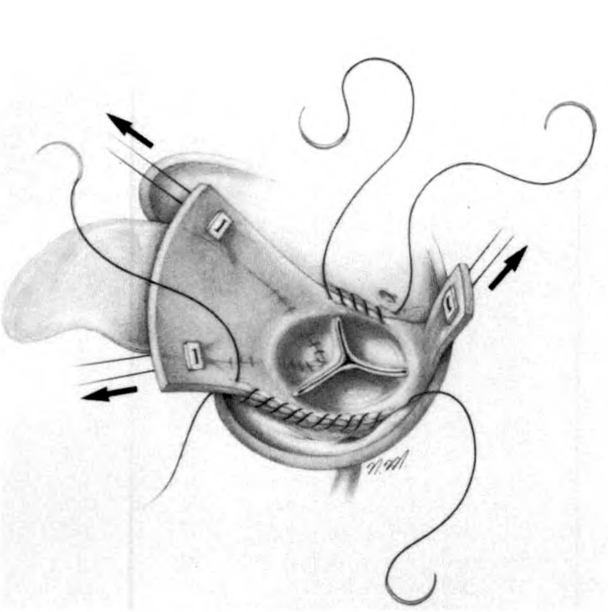

Fig 8. *Final orientation of homograft in expanded aortic root.*

(fibroblasts) of donor origin a time long after valve implantation; development of effective procurement, preservation, and distribution techniques; and reports that long-term durability of efficiently procured antibiotic-sterilized cryopreserved valves in a variety of sizes is substantially better than predicted in early reports and may approach an actuarial 10-year freedom from degeneration of close to 90% once technical problems of insertion have been overcome [4, 6, 7, 9, 12]. In addition, worldwide experience has demonstrated that thromboembolism is almost nonexistent with a homograft valve and that the incidence of endocarditis after implantation of such a valve is the lowest among all valve choices for heart valve replacement [5, 7]. It is the valve of choice for the treatment of active endocarditis [16].

In spite of improved procurement and availability, quantities are not yet sufficient to allow ABO or Rh compatibility matches between donor valve and recipient. Blood group mismatch has not been associated with a higher incidence of tissue failure to date, but as tissue preservation techniques improve, this might become a problem in the future [6, 7, 17].

Before meaningful actuarial curves of valve degeneration, freedom from reoperation, or freedom from valve-related death can be constructed, freedom from technical problems related to the operative procedure must be achieved.

Important aspects of the learning curve that are worthy of emphasis include accurate sizing of both the diameter of the annulus and the transcommissural diameter in the recipient aorta, interrupted subannular pledgeted sutures, and extensive debulking of the homograft.

Whenever the transcommissural diameter of the recipient is substantially larger than that of the aortic annulus or the homograft itself, others [9, 14, 15, 18] have suggested aortic root tailoring procedures. Barratt-Boyes and associates [9] performed this in 7.5% of patients in an early series. In the patients so treated, the aortic root was excessively large in proportion to the homograft diameter. At the Southampton hospital in England, Virdi and co-workers [14] performed aortic root tailoring in 53% of 200 patients having freehand homograft aortic valve replacement. However, early diastolic murmurs were quite frequent (28%) among patients having a tailoring procedure, and Virdi and co-workers recommended avoiding the homograft if the diameter of the recipient annulus was greater than 24 mm. The incidence of aortic regurgitation in patients having alteration (plication or excision of a strip of aortic wall) of the noncoronary sinus was also increased in the series reported by Thompson and colleagues [15]. Miller and Shumway [6] used extra material to expand the aortic root in 30% to 40% of patients in their series. In either case, whether there is plication of a large aortic root or placement of a gusset in the small aortic root, the primary objective is to maintain the cylindrical size and shape of the noncoronary sinus to prevent distortion of the homograft, poor leaflet coaptation, and subsequent aortic regurgitation.

Although excellent clinical surgeons still effectively use a continuous suture technique for the proximal subannular attachment of the homograft [7, 9, 16], Matsuki and associates [5], as well as Moreno-Cabral and co-workers [10], believe that use of interrupted sutures for the lower suture line dramatically reduces the incidence of technical failure due to malrotation. For this reason, as well as improved exposure and more secure placement, I also have used the interrupted technique.

Extensive debulking of the homograft while avoiding perforation of the muscle remnant or encroachment on the homograft leaflets is important to prevent excessive tissue in and around the coronary ostia (Fig 9). If the amount of retained septal muscle is extreme, impairment of mitral valve function can also occur, resulting in clinical mitral stenosis (Fig 10).

Technically successful implantation also depends on precise scalloping of two homograft sinuses only (retaining the noncoronary sinus), inversion of the ho-

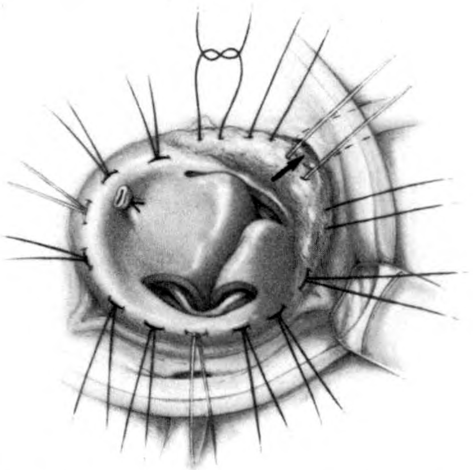

Fig 9. *Inadequate debulking of septum can produce encroachment on coronary ostia with obstruction.*

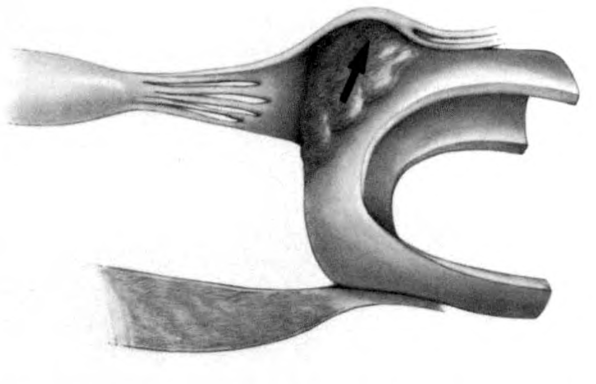

Fig 10. *Retained excessive bulk of homograft muscle can produce impairment of mitral valve function.*

mograft so that the leaflets are externally visible, setting excessive tension on the homograft commissural post above that of the native commissural attachment, and avoiding use of the homograft valve altogether when excessively large roots are encountered.

By retaining the noncoronary sinus, the spatial relationships of the other commissures are maintained, preserving the beneficial cylinder so important in avoiding valvular regurgitation [4]. Miller and Shumway [6] retain the noncoronary sinus for use as a gusset to keep the spatial relationship of the commissures. With inversion of the homograft wall, the aortic leaflets are external and are more easily protected from injury from the 3-0 needle. Exaggeration of the tension on the homograft commissural posts above the normal commissural attachments prevents prolapse of the leaflets into the ventricle once a diastolic load is imposed on the cusp edges (Fig 11).

Finally, there are anatomical conditions that dictate selection of an alternative valve substitute, and this most commonly arises when the aortic root of the recipient is excessively dilated. Although Barratt-Boyes and coworkers [9] have stated this occurs when the aortic annulus diameter is greater than 30 mm, this approach requires great experience and knowledge of aortic root tailoring procedures with their known disadvantages. In my opinion, an alternative valve should be selected whenever the aortic annulus diameter is greater than 27 mm provided at least a 25-mm homograft is readily available. The experience in two of the five instances of failure lends support to this recommendation.

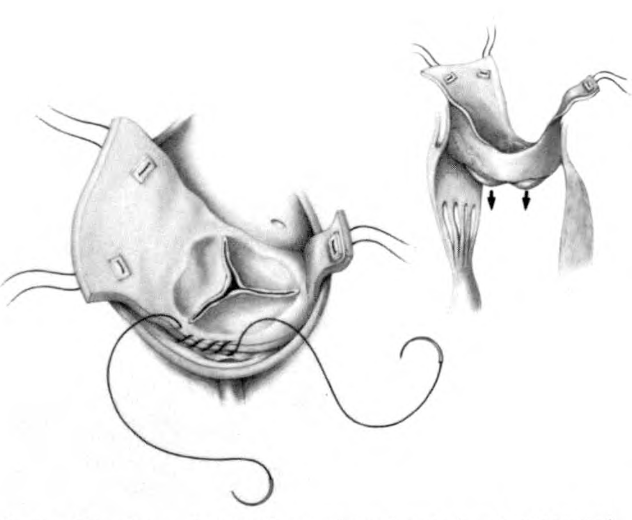

Fig 11. *If tension on homograft commissural posts is not exaggerated above (approximately 5.0 mm) native commissural attachment, prolapse of leaflets with aortic regurgitation can occur.*

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Determinants of Perioperative Morbidity and Mortality After Pneumonectomy

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A total of 197 consecutive patients undergoing pneumonectomy at the M.D. Anderson Cancer Center from 1982 to 1987 were reviewed. Sixty-five variables were analyzed for the predictive value for perioperative risk. The operative mortality rate was 7% (14/197). Patients having a right pneumonectomy (n = 95) had a higher operative mortality rate (12%) than patients having a left pneumonectomy (1%, $p < 0.05$). The extent of resection correlated with the operative mortality rate (chest wall resection or extrapleural pneumonectomy, n = 39, 15%; versus simple or intrapericardial pneumonectomy, n = 158, 5%; $p < 0.05$). Patients whose predicted postoperative pulmonary function, by spirometry and xenon 133 regional pulmonary function studies, was a forced expiratory volume in 1 second > 1.65 L, forced expiratory volume in 1 second > 58% of the preoperative value, forced vital capacity > 2.5 L, or forced vital capacity > 60% of the preoperative value had a lower operative mortality rate ($p < 0.05$). Atrial arrhythmia was the most common postoperative complication (23%). Xenon 133 regional pulmonary function studies are useful in predicting the risks of pneumonectomy.

(Ann Thorac Surg 1989;48:33–7)

Despite recent progress in chemotherapy and radiation therapy, complete resection of a tumor offers the best possibility for long-term survival in patients with lung cancer [1]. In some patients, a pneumonectomy with or without chest wall or pleural resection may be required to remove the entire tumor. Long-term survival after resection of pulmonary metastases has been well documented, and surgical resection may be a useful adjunct in the multimodality treatment of metastatic cancer [2]. In select cases, a pneumonectomy may be required for resection of the metastases. Extrapleural pneumonectomy may offer palliation and local control in some patients with pleural mesotheliomas [3].

It is well recognized that recent advances in anesthesia, intensive care, and invasive and noninvasive perioperative evaluation and monitoring have reduced the mortality rates for major pulmonary resections. However, pneumonectomy continues to be associated with the highest mortality rate for all types of pulmonary resection. In 1987, Krowka and associates [4] reported an 11% 30-day mortality rate for pneumonectomy. Weiss [1] reported a series of patients undergoing pulmonary resection for lung carcinoma with a mortality rate of 17% for pneumonectomy.

An accurate current estimation of surgical risk is useful in weighing various therapeutic options. We, therefore, undertook a review of all patients undergoing pneumonectomy at M.D. Anderson Cancer Center from July 1982 to July 1987. The purpose of the study was to define the risk factors for patients undergoing pneumonectomy and to identify subgroups of patients at higher risk with preoperative criteria.

Material and Methods

Records of 197 patients undergoing pneumonectomy at M.D. Anderson Cancer Center were available for review. One hundred sixty-one patients underwent operation for primary carcinoma of the lung, 15 for mesothelioma, 15 for metastatic disease, 3 for carcinoid, 2 for lung sarcomas, and 1 for plasma cell granuloma. The operations were performed under the direct supervision of a faculty thoracic surgeon.

Patients had a thorough preoperative evaluation to determine the tumor stage, as well as to estimate the risk of operation. All patients were evaluated by a senior staff surgeon for resectability. The patients were evaluated by the Section of Cardiopulmonary Medicine, where they underwent pulmonary function tests including regional pulmonary ventilation and perfusion using xenon 133 gas. Patients were not systematically excluded from operation based on the test results.

For the xenon 133 test, the patients were studied in an upright position at rest during normal breathing. Eight scintillation detectors were positioned against the patient's back, with four over each lung. Regional pulmonary blood flow was determined by injection of 1 to 2 mCi of xenon 133 dissolved in saline solution. Regional ventilation was determined from the distribution of a single tidal breath of xenon 133–air mixture and from the wash

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in and wash out of the equilibration volume curve using the half time in seconds [5]. Using previously described formulas [6, 7], we were able to predict lung functions after resection for these patients.

Data regarding the patients' cardiac status were retrieved, with special attention to any history of arrhythmias, coronary artery disease, hypertension, or cardiac failure. Using the criteria described by Goldman [8], a numerical value was assigned to each patient. Other preoperative variables analyzed in this study are as follows:

- General medical condition
  - Diabetes
  - Creatinine level
  - Hemoglobin level
  - Serum albumin level
- Tumor characteristics
  - Type
  - Preoperative stage
  - Final stage
- Surgical factors
  - Extent of resection
  - Additional procedures
  - Completion pneumonectomy
  - Side of resection
  - Time taken
  - Stapler use
  - Staff surgeon
  - Transfusion requirements
- Postoperative variables
  - Length of mechanical ventilation
  - Length of intensive care unit stay
  - Length of hospitalization
  - Pulmonary edema
  - Bronchopleural fistula
  - Atelectasis
  - Wound infection
  - Other complications

Patients dying within 30 days of operation or during the same hospitalization were considered operative deaths. Based on the clinical course of the patients, we were able to classify five deaths as resulting from cardiac causes, two deaths from pulmonary causes, six deaths from cardiopulmonary causes, and one death from technical causes.

All postoperative and intraoperative complications, regardless of their impact on the hospital stay, were noted. These included arrhythmias, premature ventricular contractions, pulmonary edema, pneumonia, bronchopleural fistula, wound infections, intubation longer than 48 hours, atelectasis, and secretions requiring therapeutic bronchoscopy.

The necessity for pneumonectomy was determined by the staff surgeon at the time of operation. All patients with primary lung cancer underwent complete lymph node mapping. The extent of resection was primarily determined by the tumor size and local extension. In this series, 92 patients (46%) had a simple pneumonectomy with lymph node dissection, whereas 66 patients (34%) had an intrapericardial pneumonectomy. The other 39 patients (20%) required resection of the chest wall, pleura, or diaphragm.

Eighteen patients (10%) had prior pulmonary resection and had a completion pneumonectomy. In addition, 39 patients had mediastinoscopy, 5 had an anterior mediastinotomy, 2 had a concomitant tracheostomy, 1 had a staging adrenalectomy, 1 had a concomitant thymectomy, and 2 were operated on via a midline sternotomy incision.

The incidence of surgical complications including deaths was compared for patients according to the demographic and disease characteristics, pulmonary functions, and surgical variables. Differences were compared by χ^2 tests. All p values are two-tailed.

Results

The mean (± standard error of the mean) age of patients in this series was 55 ± 0.8 yr. There were 137 men and 60 women. The mean postoperative hospital stay was 10 ± 0.4 days; the mean intensive care unit stay was 3 ± 0.2 days. Patients required a mean of 36 ± 5 hours of mechanical ventilation.

The mortality rate was 7%, and this was not significantly influenced by age, sex, or Goldman criteria (Table 1). Patients who had a right pneumonectomy had a higher operative mortality rate (12%) compared with patients who had a left pneumonectomy (1%) ($p < 0.05$). This difference was independent of other factors.

Patients who had chest wall resection, extrapleural pneumonectomy, or resection of the diaphragm had a mortality rate of 15%, compared with 5% for patients who had a simple or intrapericardial pneumonectomy ($p < 0.05$).

Transfusion requirements greater than 3 units increased the operative mortality rate from 4% to 17% ($p < 0.05$). However, there was a statistically significant correlation between the extent of resection and transfusion requirements, indicating that transfusion was not an independent determinant of operative mortality. The mean total volume of fluids given during the perioperative period (24-hour period after induction of anesthesia) was 5.4 ± 0.8 L. The total volume of fluid was not significantly increased in those patients who died after operation. The volume of fluids given perioperatively did not differ significantly for patients receiving a right compared with left pneumonectomy.

Patients undergoing a completion pneumonectomy had a mortality rate of 11% compared with 6.7% for other patients. This difference was not statistically significant.

Patients with a preoperative forced vital capacity (FVC) less than 85% of the preoperative predicted normal value had a mortality rate of 11%, which was significantly ($p < 0.05$) higher than that of patients with an FVC greater than or equal to 85% of predicted (3%). We were unable to show any statistically significant differences in mortality based on preoperative forced expiratory volume in 1 second (FEV_1), ratio of FEV_1/FVC, absolute FVC, or forced expiratory flow (FEF).

Using the regional ventilation perfusion studies and standard pulmonary function tests, we calculated the

Table 1. Differences in Operative Mortality for Various Criteria

Criterion	No. of Deaths/ No. of Patients	Mortality (%)	p Value[a]
Age			NS
<70 years	12/181	6.6	
≥70 years	2/16	13	
Sex			NS
Male	12/137	9	
Female	2/60	3	
Goldman's criteria			NS
≤9	11/176	6	
>9	1/21	14	
Side			<0.05
Right	13/95	14	
Left	1/102	1	
Extent of resection			<0.05
Simple	4/92	4	
Intrapericardial	4/66	6	
Extended	6/39	15	
Transfusions			<0.05
None	3/93	3	
1–3	4/64	6	
>3	7/40	18	
Completion pneumonectomy	18	11	NS

[a] Determined by χ^2 analysis.

NS = not significant.

predicted postresection FEV_1 and FVC (Table 2). Patients with a predicted postoperative FEV_1 of 1.65 L or more had no perioperative deaths, compared with a perioperative mortality rate of 9% in patients with a lower predicted FEV_1 ($p < 0.05$). Patients with a predicted FEV_1 less than 41% of normal had a mortality rate of 16% compared with a mortality rate of 3% for patients with a predicted FEV_1 greater than or equal to 41% of normal.

Patients with a predicted postoperative FVC greater than or equal to 2.13 L had a mortality rate of approximately 2.5% compared with 11% in patients with a lower predicted FVC ($p < 0.05$). Patients with a predicted postoperative FVC greater than or equal to 51% of normal had a mortality rate of approximately 1% compared with 12% in patients with a lower predicted FVC ($p < 0.05$). Additional procedures such as mediastinoscopy and mediastinotomy did not adversely affect mortality rate.

Atrial arrhythmias were the most common complication, occurring in 46 patients (23%). Atrial arrhythmias were seen in 23% of patients undergoing simple pneumonectomy compared with 20% of patients requiring intrapericardial dissection (not significant). Patients who developed atrial arrhythmias had a longer stay in the intensive care unit (4.8 versus 2.5 days) and a longer postoperative hospital stay (13.7 versus 9.3 days) compared with patients who did not develop atrial arrhythmias ($p < 0.05$).

Patients undergoing simple pneumonectomy had a 36% incidence of complications compared with 53% for intrapericardial resection. Other procedures such as chest wall resection, extrapleural pneumonectomy, and diaphragm resection increased the complication rate to 67%.

The incidence of all nonfatal complications increased with the number of transfusions required. Patients who required no transfusion had a 39% incidence of complications, whereas patients requiring three or more transfusions had a 61% incidence of complications. Because of the correlation between extent of resection and transfusion, the transfusion requirement was not an independent predictor of operative complications. We were unable to show any significant effect of age, sex, preoperative lung function tests, or predicted lung function on the incidence of all postoperative complications.

Cardiac failure developed in 18 patients (9%), showing no correlation with age or Goldman's criteria. Eighteen patients required ventilation longer than 48 hours. These patients had a mean preoperative FEV_1 of 69% of predicted normal compared with a mean preoperative FEV_1 of 79% of predicted normal for patients requiring ventilation for 48 hours or less ($p < 0.05$). No significant differences in other measures of preoperative spirometry could be demonstrated. However, when analyzing predicted postoperative lung function, significant differences were noted (Table 3). Patients requiring prolonged ventilation had a mean predicted FEV_1 of 43% of normal compared with 48% ($p < 0.05$) and mean predicted FVC of 45% compared with 52% ($p < 0.05$) for patients requiring mechanical ventilation for 48 hours or less. Other pulmonary complications, such as major atelectasis, pneumonia, and retained secretions, occurred in 13 patients (6.6%).

Technical complications such as excessive blood loss (>6 units), loss of arterial or venous control, failure of the stapler to fire correctly, and inadvertent injury to unrelated structures occurred in 13 patients (6.6%). Eight patients (4%) developed a bronchopleural fistula. All bronchopleural fistulas developed on the right side ($p < 0.05$).

Table 2. Predicted Postoperative Lung Function

Variable		No. of Patients	Deaths[a]	p Value[b]
FEV_1 (L)	≥1.65	47	0 (0)	<0.05
	<1.65	126	12 (9)	
FVC (L)	≥2.13	78	2 (2.5)	<0.05
	<2.13	95	10 (11)	
Percent FEV_1	≥41%	122	4 (3)	<0.05
	<41%	51	8 (16)	
Percent FVC	≥51%	83	1 (1)	<0.05
	<51%	90	11 (12)	

[a] Numbers in parentheses are percentages. [b] Determined by χ^2 analysis.

FEV_1 = forced expiratory volume in 1 second. FVC = forced vital capacity.

Table 3. Lung Function in Patients Requiring Prolonged Ventilation

Variable	Ventilation[a]		p Value[b]
	>48 Hours (n = 18)	≤48 Hours (n = 179)	
Percent predicted normal FEV_1 (preoperative)	69% ± 0.04%	79% ± 0.01%	<0.05
Predicted (postoperative) FEV_1 (L)	1.26 ± 0.04	1.49 ± 0.07	<0.05
Percent predicted (postoperative) FEV_1	43% ± 0.02%	48% ± 0.01%	<0.05
Predicted (postoperative) FVC (L)	1.93 ± 0.12	2.08 ± 0.05	NS
Percent predicted (postoperative) FVC	45% ± 0.02%	52% ± 0.01%	<0.05

[a] Data are reported as mean ± standard deviation. [b] Determined by Student's t test.

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; NS = not significant.

Comment

Two large series [4, 9] describing the risks of pneumonectomy have recently been published. One multicenter study [9] reported a mortality rate of approximately 7% for patients undergoing simple pneumonectomy for carcinoma of the lung. The other series [4] described patients with a variety of diseases that required a pneumonectomy. The mortality rate in that series was 13%. Our mortality rate of 7% is consistent with these and earlier reports [10].

In a separate study, Reichel [10] showed no significant increase in mortality related to age. Kohman and associates [11] reported an increase in the operative mortality rate from 2.4% for patients younger than 60 years of age to 7.4% in patients older than 60 years. This study considered all types of lung resections. Ginsberg and co-workers [9] reported an increased mortality rate in patients older than 70 years. However, further analysis of their data for pneumonectomies alone shows a mortality rate of 5.9% for patients older than 70 years compared with 8% in patients younger than 70 years.

Our results show no significant increase in mortality related to age. Reviewing patients older than 70 years of age, Breyer and co-workers [12] reported a mortality rate of 5% in patients with either lobectomy or pneumonectomy. The increased risk associated with right pneumonectomy is documented in various publications [10, 13, 14].

Gerson [15] reported a higher mortality rate in patients with a preoperative FEV_1 of less than 70% of the predicted normal value. Similar results were reported independently by Boushy and co-workers [16]. However, Keagy and associates [17] reported no significant effects of preoperative FEV_1 and FVC on mortality. In this study, ventilation perfusion scans were not performed and no attempt was made to estimate postresection lung function.

In an experimental clinical study, Adams and colleagues [18] showed the importance of cardiopulmonary reserve as a determinant of risk. Since then, many investigators have reported the effects of tests of predicted postresection lung function on mortality. Earlier studies were done using a double-lumen Carlen tube placed under local anesthesia. Neuhaus and Cheriack [19], in such a study, showed good correlation between predicted lung function and complications.

The introduction of ventilation perfusion studies using xenon 133 gas obviated the need for double-lumen tubes for such tests. Various investigators [6, 7] have reported the technique and the reliability of these studies in calculating predicted lung function. These predictors are very useful clinically because regional and overall pulmonary functions remain stable after pneumonectomy [20]. In our series, we were able to show significant differences in mortality based on predicted lung function.

The incidence of atrial arrhythmias after pneumonectomy varies from 6% to 29% in various series [21, 22]. We report an incidence of 23%, but were unable to demonstrate any differences based on the extent of resection.

This study shows that the operative mortality rate after pneumonectomy has not changed greatly over the last two decades. Most of the deaths in this series were from cardiac and cardiopulmonary causes.

Using the preoperative xenon 133 regional ventilation and perfusion studies in conjunction with overall pulmonary function tests and demographic criteria, we are able to identify patients at higher risk. These patients should receive more intensive perioperative evaluation and hemodynamic monitoring to reduce their operative risk. Such efforts should primarily be directed at the cardiopulmonary system. Furthermore, the risk of operation must be carefully balanced with a better chance for survival in patients requiring extended resection.

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Does Hypothermic Fibrillatory Arrest Improve Myocardial Protection During Emergency Revascularization?

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Hypothermic fibrillatory arrest (HFA) was compared with conventional hypothermic cardioplegic arrest (HCA) in a model of acute regional ischemia. In 20 pigs, the left anterior descending coronary artery was occluded for 30 minutes before cardiopulmonary bypass. In the HCA group (n = 10), the heart was arrested with a hyperkalemic cold crystalloid solution, whereas in HFA animals (n = 10), the heart was vented and allowed to fibrillate spontaneously without cross-clamping. Miniature pH probes monitored intramyocardial pH during 45 minutes of arrest (HCA or HFA, both with systemic and topical myocardial cooling) and during two hours of coronary reperfusion. Hypothermic fibrillatory arrest did not ameliorate the acidosis in the ischemic (left anterior descending) region; indeed, after two hours of coronary reperfusion, there was a trend toward more acidosis in the postischemic left anterior descending territory in the HFA group. However, HFA did prevent acidosis in the nonischemic (left circumflex) territory. Infarct size expressed as percent of region at risk was 18.1% ± 3.2% (mean ± standard error of the mean) in the HCA animals and 18.8% ± 4.4% in the HFA animals. These results demonstrate that HFA offers no advantage over HCA in protection of regionally ischemic myocardium in a model with minimal collateral circulation.

(Ann Thorac Surg 1989;48:38–42)

For most patients undergoing cardiac operations, current techniques of hypothermic cardioplegic arrest (HCA) preserve ventricular function well. Profound cardiac cooling and the immediate chemical induction of electromechanical arrest permit extended periods of cardiac arrest with excellent metabolic and mechanical recovery. However, in certain subsets of patients these techniques of myocardial protection remain inadequate. Patients with acute and ongoing myocardial ischemia, such as those with an evolving myocardial infarction or those with complications from failed percutaneous transluminal coronary angioplasty, are at high risk for low cardiac output after emergency revascularization. Recent clinical reports on urgent surgical revascularization for acute ischemia have documented higher operative mortality, higher perioperative myocardial infarction rate (even with rapid transit to the operating room), and greater need for postoperative inotropic or mechanical support [1, 2].

Previous studies from this laboratory have demonstrated that when ischemic myocardium is subjected to hypothermic global ischemic arrest, myocardial salvage is adversely affected [3, 4]. Therefore, any technique that minimizes or obviates the global ischemic insult of aortic cross-clamping might result in superior myocardial protection.

Several clinical series using the technique of hypothermic fibrillatory arrest (HFA) have suggested that HFA may be an effective alternative strategy for myocardial protection [5–7]. Typically, the technique involves performance of proximal aortosaphenous anastomoses before cardiopulmonary bypass (CPB), followed by rapid systemic cooling on CPB. Systemic arterial pressure on CPB is kept high, usually above 80 to 90 mm Hg. Topical myocardial cooling and elective ventricular fibrillation provide a nearly still heart for the distal coronary anastomoses [5]. Advocates propose that HFA avoids the global ischemic insult of aortic cross-clamping and leads to earlier reperfusion of the most ischemic region. The excellent clinical results reported in high-risk patients undergoing emergency procedures [8] led us to examine whether this technique compares favorably with standard HCA in an animal model of acute regional ischemia. This model simulates emergency surgical revascularization for acute myocardial ischemia.

Material and Methods

Male and female farm pigs weighing 25 to 35 kg were premedicated with intramuscular ketamine hydrochloride (40 mg/kg) and anesthetized with intravenous sodium pentobarbital (30 mg/kg). Animals were intubated and maintained on a Harvard ventilator, with adjustments made to achieve a Po_2 of 100 to 200 mm Hg, Pco_2 near 40 mm Hg, and pH of 7.40. Polyethylene catheters were inserted in the external jugular vein and common carotid artery to monitor central venous and arterial pressure. Intravenous bretylium tosylate (2 mg/kg) was adminis-

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tered to prevent ventricular fibrillation during median sternotomy and exposure of the heart.

Regional myocardial protection was assessed by on-line monitoring of myocardial tissue pH. Subminiature pH electrodes (Ingold Electrodes, Inc, Andover, MA) were placed at two locations near the center of the region at risk (left anterior descending distribution) and in one location in the posterolateral left ventricular wall (left circumflex distribution). The Khuri Regional Tissue Ischemia Monitor (Vascular Technology, Inc, 1 North Chelmsford, MA) [9, 10] calculated actual tissue pH based on prior calibration and simultaneous regional myocardial temperature. Thirty minutes of equilibration time were allowed after placement of the pH probes to minimize effects of local tissue damage produced by pH probe insertion.

To create reversible regional ischemia, the left anterior descending coronary artery was occluded with an atraumatic vascular clip just distal to the first large diagonal branch. Hearts that fibrillated during ischemia were defibrillated quickly with a direct current countershock. After 30 minutes of normothermic regional ischemia, all animals were heparinized and connected for CPB using a 28F venous cannula in the right atrium and a 14F arterial cannula in the left femoral artery. A Harvey H-1500 bubble oxygenator primed with 1 L of homologous blood completed the CPB circuit.

In the HCA animals (n = 10), the aorta was cross-clamped and the heart arrested with an aortic root injection of 250 mL of 4°C hyperkalemic crystalloid cardioplegic solution. In the HFA group (n = 10), the heart was vented via the left ventricular apex and allowed to fibrillate spontaneously without cross-clamping. In both groups, topical iced saline solution maintained myocardial temperature below 15°C, as measured by needle thermistor probes. All animals were cooled to a systemic temperature of 28°C.

In both groups, after the 45-minute arrest period the coronary artery occluder was removed, simulating surgical revascularization. Animals were weaned from CPB over the next 45 minutes without the use of inotropic drugs. Frequent measurements of arterial blood gases were made to insure normal values; sodium bicarbonate was given to correct metabolic acidosis if present.

After two hours of reperfusion, the pH probes were removed and the region at risk for ischemic injury was determined by intracoronary injection of monastryl blue dye (B.W. 372-P phthalo-blue B, DuPont De Nemours Company, Wilmington, DE). The right ventricle and atria were removed and the left ventricle was cut into 1-cm slices in a plane parallel to the atrioventricular groove. Slices were incubated in a 1% solution of nitro blue tetrazolium chloride (Polysciences, Warrington, PA) for 20 minutes at 37°C to determine if infarction had occurred. Cross-sectional areas of the region at risk and infarction were determined by planimetry.

Values are reported as mean ± the standard error of the mean. The sizes of the region at risk and the infarction were compared by the nonparametric Wilcoxon rank sum test. All regional pH values were corrected to 37°C by the following formula: pH(corrected) = pH(measured) + 0.015 (T − 37), where T is myocardial temperature in degrees centigrade. The pH trends were compared by an analysis of variance for repeated measures. Arrest and reperfusion phases were examined separately.

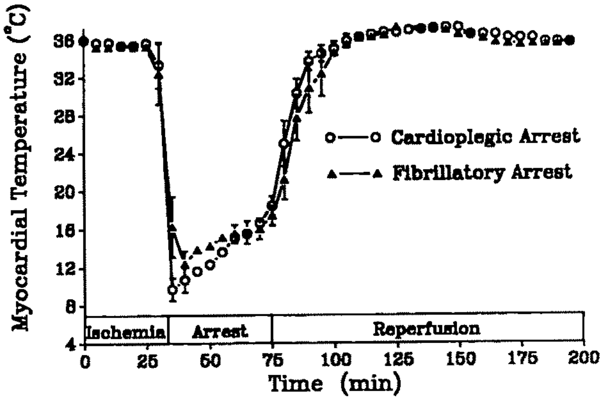

Fig 1. Myocardial temperature in the nonischemic region (left circumflex territory) during cardioplegic versus fibrillatory arrest.

All animals received humane care according to the "Guidelines for the care and use of laboratory animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH publication No. 85-23, Revised 1985).

Results

There were no significant differences between HFA and HCA groups in physiological variables, including hematocrit, arterial blood gases, and mean perfusion pressure on CPB. All but two animals (one in each group) had at least one episode of ventricular fibrillation during the 30-minute period of regional ischemia. In all cases, it was possible to restore sinus rhythm by defibrillation before the myocardial arrest period. No animals were excluded from the study.

Figure 1 depicts the time course of myocardial temperature for the two groups recorded at 5-minute intervals during the study. In the nonischemic area of the left ventricle there were no statistically significant differences in temperature between HFA and HCA groups during the prebypass, arrest, or reperfusion periods. However, there was a trend toward warmer myocardial temperatures in the HFA group during the arrest procedure.

In Figure 2 are the average temperatures of the two probes placed in the ischemic region. No significant temperature differences were seen between the HFA and HCA groups during any phase of the study, as determined by analysis of variance for repeated measures.

Displayed in Figure 3 are the pH measurements made in the nonischemic area, corrected to 37°C. Although the curves appear similar during the period of regional ischemia, there was significantly greater myocardial acidosis during the arrest and reperfusion periods in the HCA group. At the conclusion of the myocardial arrest period, mean pH in the HCA group was 6.92 ± 0.04 compared with 7.20 ± 0.06 in the HFA group. This trend of more acidosis in HCA animals persisted in the reperfusion period, although by the end of reperfusion, mean pH in both groups converged to 7.29 ± 0.04.

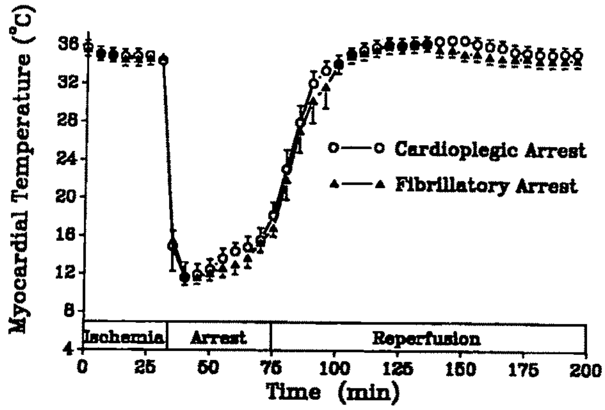

Fig 2. Myocardial temperature in the ischemic region (left anterior descending territory) during cardioplegic versus fibrillatory arrest.

Figure 4 shows the time course of tissue pH in the ischemic region. At the conclusion of myocardial arrest, myocardial pH in the two groups was similar: 5.87 ± 0.10 for HCA animals and 5.88 ± 0.05 for the HFA animals. However, during coronary reperfusion there was a trend toward more myocardial acidosis in the HFA group, with a final pH of 6.92 ± 0.09 compared with 7.19 ± 0.06 in HCA animals.

The two experimental groups had comparable areas of the left ventricle at risk for ischemic injury: 30.5% ± 2.1% in HCA and 30.9% ± 2.4% in HFA animals (Fig 5). Infarct sizes measured by vital staining and expressed as percent of the region at risk were also similar: 18.1% ± 3.2%, in the HCA and 18.8% ± 4.4% in the HFA animals. Myocardial necrosis was not seen in any area outside the region at risk.

To evaluate the usefulness of regional intramyocardial pH measurements, the minimum pH reached during ischemia and a mean pH during reperfusion were correlated with the eventual infarct size. As shown in Figures 6 and 7, these correlations were both quite poor ($r = -0.31$ and $r = -0.25$, respectively).

Comment

Surgical revascularization for rapidly progressive unstable angina, evolving myocardial infarction, and persistent ischemia after infarction has a higher overall mortality rate than routine coronary revascularization [11–15]. A growing body of experimental and clinical evidence has helped to explain the increased risk of perioperative injury. With ongoing ischemia before operation, the myocardium has less metabolic reserve and, therefore, increased susceptibility to further injury. Although standard intraoperative myocardial protective techniques have been refined to minimize gobal ischemic injury, the added insult of aortic cross-clamping may allow the evolving infarction to continue to enlarge, creating greater irreversible injury. In addition, reperfusion of the ischemic myocardium likely contributes to further necrosis due to lipid peroxidation of cellular membranes by oxygen radicals, the influx of calcium into impaired cells, and the immediate functional demands placed on the injured myocardium during reperfusion.

Studies carried out in our laboratory using a porcine model of reversible regional ischemia have allowed us to examine the role of various interventions that might limit both infarct extension and postischemic ventricular dysfunction. In hearts subjected to mid-left anterior descending coronary artery occlusion followed by global ischemia and reperfusion, the administration of superoxide dismutase was effective in reducing infarct size [16] and in

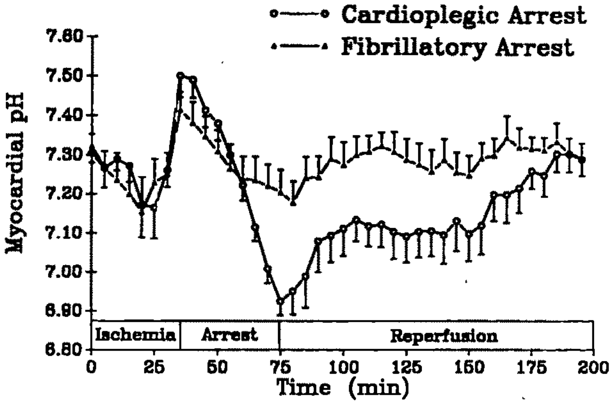

Fig 3. Myocardial pH in the nonischemic region (left circumflex territory) during cardioplegic versus fibrillatory arrest.

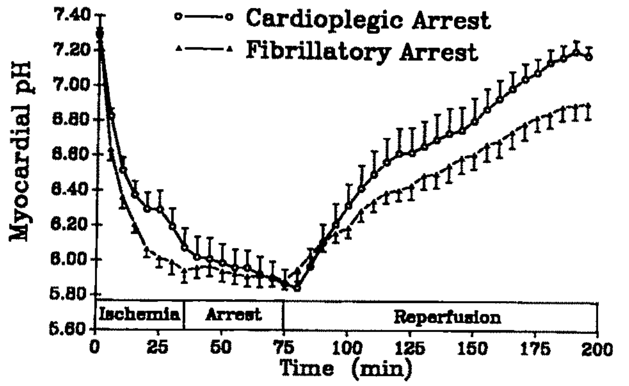

Fig 4. Myocardial pH in the ischemic region (left anterior descending territory) during cardioplegic versus fibrillatory arrest.

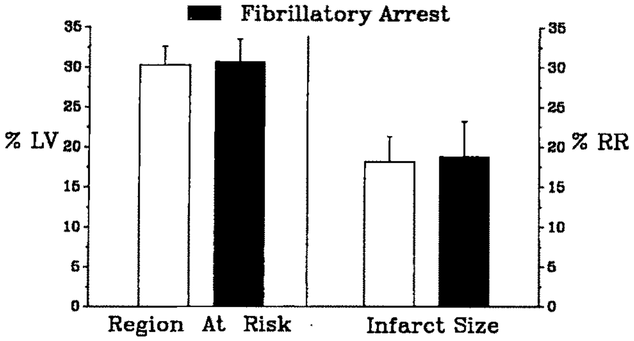

Fig 5. Region at risk (RR) for infarction and size of infarction after regional ischemia: cardioplegic versus fibrillatory arrest. (Left) Region at risk expressed as percent of left ventricular (LV) mass, cardioplegic versus fibrillatory arrest. (Right) Infarct size expressed as percent of region at risk, cardioplegic versus fibrillatory arrest.

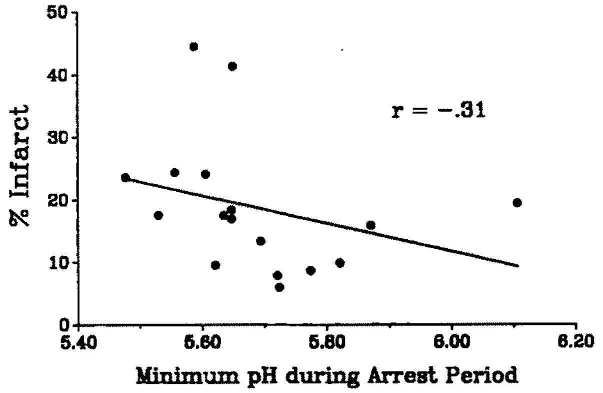

Fig 6. Relationship of minimum myocardial pH during myocardial arrest to eventual infarction size (data from both cardioplegic and fibrillatory arrest groups).

limiting postischemic ventricular dysfunction [17]. Even more dramatic improvement was observed in this porcine model when a superoxide dismutase-enriched solution was administered via the coronary sinus during the global ischemic period [18].

This porcine model of regional ischemia has also enabled definition of the time course of infarction and the reliability of vital staining techniques for measurement of infarct size [19]. Although the frequency of ventricular tachyarrhythmias makes the pig a challenging experimental animal, we prefer the porcine model because the end-artery coronary pattern more closely resembles the circulation of the human heart than does the more extensively collateralized canine heart. This experimental model of emergency revascularization is analogous to failure of percutaneous transluminal coronary angioplasty (sudden and total coronary occlusion) in a patient lacking well-developed collateral myocardial blood flow.

The present study was undertaken to examine the hypothesis that hypothermic fibrillatory arrest is peferable to cardioplegic arrest in hearts with preexisting regional ischemia. Theoretically, the operative strategy of HFA avoids the additive insult of global ischemia as the aorta is not cross-clamped and coronary artery perfusion (except in the region at risk) is maintained. If there are zones of myocardium within the region at risk that are on the threshold of necrosis but are still salvageable, maintenance of myocardial perfusion during bypass grafting might result in ultimate infarct reduction.

The safety and clinical efficacy of HFA has been well documented in clinical reports by Akins and associates [5–8, 20–22]. In a recent review of 1,000 consecutive patients undergoing nonemergency coronary artery bypass grafting with HFA between 1979 and 1984, Akins and Casoll [22] reported a hospital mortality of only 0.4% and a perioperative myocardial infarction rate of 1.8%. Survival at 5 years in this patient group was 91.6% and actuarial event-free rates at 5 years were 97.7% for myocardial infarction, 99.4% for percutaneous transluminal coronary angioplasty, 99.5% for reoperative revascularization, and 88.6% for all combined morbidity and mortality. Even more remarkable were results reported in high-risk emergency patients managed with HFA [8]. In 127 consecutive patients who required emergency myocardial revascularization, there was only one hospital death (0.8%) and a single perioperative myocardial infarction (0.8%). Actuarial survival at 45 months was 90.8%, and the mean New York Heart Association classification for the 117 long-term survivors was 1.12.

The definition of an "emergency operation" in this study was broad. Included as emergencies were patients whose operations were performed outside normal operating room hours and patients whose deteriorating clinical condition required cancellation of an elective procedure. Nonetheless, this report and other successes with patients having left ventricular aneurysms [21] demonstrate that HFA can be used safely in a broad range of clinical circumstances. As Akins and Casoll [22] note, the efficacy of HFA challenges the view that refinements in myocardial preservation with HCA have been the reason for improved results with coronary bypass grafting.

In addition to avoiding the global ischemia that accompanies cardioplegic techniques, HFA can be expected to have other possible benefits in special circumstances. Avoidance of aortic cross-clamping is especially critical in patients with severe calcification of the ascending aorta. This problem has become increasingly frequent as older patients become surgical candidates. Also, in patients at risk of postoperative right ventricular dysfunction, HFA would seem ideal because coronary perfusion can be maintained during revascularization.

However, there are theoretical problems with the clinical use of HFA. As described by Akins, in contrast to the usual technique of HCA, with HFA proximal aortosaphenous anastomoses must be performed before CPB, requiring the placement of a partial occlusion clamp on the aorta. Potentially, this may increase afterload and oxygen demand on a heart already stressed by inadequate coronary blood flow [23]. These partial aortic occlusions also introduce risk of embolization of arteriosclerotic debris to the coronary and cerebral circulations. Also, with HFA the surgeon loses the bloodless, quiet surgical field achieved with cardioplegic arrest.

Few experimental data have been available to compare

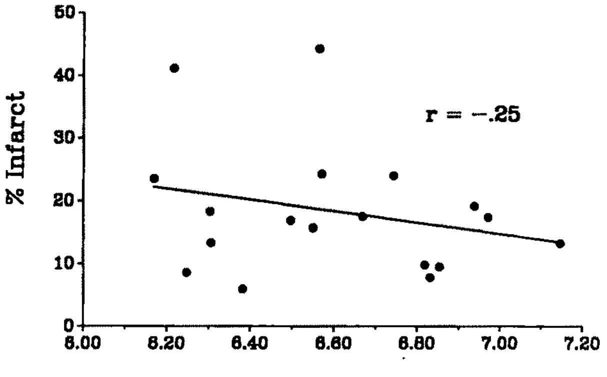

Fig 7. Relationship of mean pH during coronary reperfusion to eventual infarction size (data from both cardioplegic and fibrillatory arrest groups).

HFA and HCA [23]. This study was undertaken because we believed that if HFA provided better salvage of myocardial tissue with evolving ischemia, disadvantages of the technique could be tolerated. In a porcine model of regional ischemia and simulated emergency revascularization, HFA was no better than HCA at preventing necrosis in jeopardized myocardial tissue. Furthermore, although there was evidence that HFA prevented intramyocardial acidosis, as assessed by continuous pH monitoring, this benefit was observed only in nonischemic regions of the heart and not in areas of preexisting ischemia which were at risk of infarct extension. Interestingly, there was no marked difference between groups in the temperatures recorded in the nonischemic region, despite the HFA group having no cross-clamp. This likely reflects the remarkable efficiency of topical cooling, especially in the thin-walled porcine myocardium.

These data confirm clinical reports that HFA is a safe method of myocardial protection: postoperative infarcts were no larger in animals subjected to HFA. However, HFA was not superior to hypothermic cardioplegic techniques in this model of acute regional ischemia in which there is little or no collateral coronary blood flow. The most useful role for HFA may be in situations in which the aorta cannot be safely cross-clamped because of severe aortic calcification and the attendant high risk of embolic injury.

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Stage I Palliation of Hypoplastic Left Heart Syndrome: The Importance of Neoaorta Construction

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After Norwood's initial report of successful first-stage palliation of hypoplastic left heart syndrome in neonates, the occurrence of distal aortic obstructions, shunt problems, and late deaths have led to modifications in the surgical technique. Between January 1986 and December 1987, 12 neonates from three to 16 days old underwent stage I palliation with the same objectives. An open atrial septectomy was always performed. The pulmonary artery bifurcation was transected from the main pulmonary artery and closed with an aortic homograft patch. The aortotomy was begun 2 cm below the patent ductus arteriosus insertion and extended across the transverse arch and down the ascending aorta. The neoaorta was constructed using the hypoplastic ascending aorta–transverse aortic arch, the main pulmonary artery, and an aortic homograft augmentation patch. The homograft is hemostatic and pliable, and molds well in forming the neoaorta. A 4-mm shunt was inserted between the right innominate artery and the right pulmonary artery in 5 patients and the neoaorta and the pulmonary artery bifurcation patch in 7 patients. The early systemic oxygen saturation was optimized at 75% to 80% with hyperventilation, high concentration of inspired oxygen, sodium bicarbonate, and the frequent use of vasopressors to maintain an arterial blood pressure of 65 to 75 mm Hg. Two patients (17%) died early after operation; 1 had severe right ventricular dysfunction and both had severe tricuspid regurgitation. There were 2 late deaths at 7 and 13 months, of sepsis and hypoxia. The 8 survivors (67%) continue to do well over follow-up. The preoperative tricuspid regurgitation has remained stable in 3 survivors and disappeared in 2 survivors. Critical attention to construction of the neoaorta and careful ventilatory and pharmacological management of the ratio of pulmonary to systemic vascular resistance has led to improved survival after stage I palliation.

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Hypoplastic left heart syndrome (HLHS) is one of the last frontiers in congenital heart disease. Though its incidence is only 1% of all congenital cardiac anomalies, HLHS accounts for nearly 25% of all cardiac-related deaths during the first week of life [1]. In the most complex form, the central anatomical feature is aortic valve atresia, associated with severe hypoplasia of the ascending aorta, atresia or severe hypoplasia of the mitral valve, and a diminutive or absent left ventricle [2]. Lev and associates [3] postulated that abnormal formation of the foramen ovale leads to faulty transfer of blood from the inferior vena cava to the left atrium in fetal life and underdevelopment of the left heart. Systemic blood flow is maintained by the right ventricle through the ductus arteriosus, determined by the relative resistances of the pulmonary and systemic vascular beds.

The hemodynamics in the developing fetus with HLHS are perfectly adequate to allow otherwise normal growth and development of the fetus. Cardiac anomalies not part of the aortic atresia complex are rare. Early neonatal death usually results from inadequate coronary and systemic perfusion secondary to ductal closure and increasing pulmonary blood flow as the pulmonary vascular resistance decreases in the early postnatal period. Less commonly, death results from hypoxemia and pulmonary venous congestion secondary to a very restrictive interatrial communication. Over 95% of infants with HLHS die within the first month of life, most within the first week [4]. Medical therapy is largely supportive and does not appreciably alter the uniformly fatal outcome.

Physiological correction of HLHS is possible only by separation of the pulmonary and systemic circulations using the right ventricle as the systemic pumping ventricle. Circulation of blood through the pulmonary vasculature without a pulmonary ventricle can only be achieved if the pulmonary vascular resistance is low, as it is in the normal mature lung [5]. However, in the newborn period, pulmonary vascular resistance is elevated and may not decrease to adult levels until the infant is 6 to 8 weeks of age. Furthermore, a postmortem quantitative pulmonary morphometric analysis has demonstrated pulmonary vascular changes that are likely to result in elevated neonatal pulmonary vascular resistance [6]. Thus, physiological correction is precluded in the neonatal period, precisely when most patients with HLHS become symptomatic and

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die. A number of palliative procedures have been reported to prepare these children for a modified Fontan procedure [7–12].

In 1983 Lang and Norwood [13] reported on a palliative operation for HLHS with follow-up cardiac catheterization to ascertain the patient's suitability for a Fontan procedure. The objectives of stage I palliation derived from that experience included (1) establishment of an unobstructive communication between the right ventricle and the descending aorta to allow for adequate systemic perfusion and to preserve ventricular function, (2) creation of a large interatrial communication, (3) limitation of pulmonary blood flow to allow for the normal postnatal development of the pulmonary vasculature, and (4) avoidance of distortion of the branch pulmonary arteries to facilitate later physiological correction. Subsequently Norwood and associates [14] reported on the first successful application of Fontan's procedure after stage I palliation, thus establishing the feasibility of the two-stage reconstructive approach to HLHS. Since that time, continued modifications in the surgical technique and perioperative care have occurred to minimize early mortality, reduce late complications, and optimize the patient's anatomy and physiology for a subsequent Fontan procedure [15, 16]. This report reviews our recent experience with stage I palliation, emphasizing several technical modifications and the importance of perioperative care.

Material and Methods

From January 1986 through December 1987, 12 consecutive nonselected infants (11 male, 1 female) ranging in age from three to 16 days (median age, 5 days) and weighing 2.5 to 3.7 kg underwent a stage I palliative reconstructive operation for HLHS. By two days of age (range, one to three days) most newborns were sufficiently symptomatic to attract medical attention. The most striking physical finding was poor peripheral perfusion with delayed capillary refill, although a heart murmur was heard in all patients and central cyanosis was usually present.

The preoperative electrocardiograms reflected sinus rhythm with underdevelopment of the left side of the heart and prominence of right-sided forces. The chest roentgenograms demonstrated moderate cardiomegaly in 10 patients and severe enlargement in 2 patients who had severe tricuspid regurgitation. Pulmonary vascular markings were always increased.

Two-dimensional echocardiography with Doppler investigation was routinely used to confirm the diagnosis of HLHS and define the anatomical details. Hypoplasia of the ascending aorta was characteristically marked in all patients (1 to 4 mm in diameter). The ascending aorta tapered down to the aortic annulus and coronary arteries in the 6 (50%) patients with aortic atresia and in the 6 patients (50%) in whom the aortic valve was small but perforate. The mitral valve was atretic in 3 patients and quite hypoplastic in 9 patients. Severe mitral hypoplasia was present in 4 of 6 (66%) patients with aortic atresia and intact ventricular septum. The ascending aorta tended to be smaller in the 2 patients with mitral atresia and aortic atresia. The transverse aortic arch was usually slightly larger than the ascending aorta.

Table 1. Preoperative Echocardiography

Tricuspid Regurgitation	Right Ventricular Function: Good	Borderline	Poor	Total
None	3	2	0	5
Moderate	1	2	2	5
Severe	0	1	1	2
Total	4	5	3	12

The size of the left ventricle was dependent on the status of the ventricular septum and the state of the mitral valve. In 2 patients with intact ventricular septum and mitral atresia, the left ventricle was a slit-like chamber. When the ventricular septum was intact and the mitral valve was perforate, the left ventricle was markedly hypoplastic (9 patients). Endocardial fibroelastosis in the left ventricle was seen in 2 patients. In 1 patient with mitral atresia, severe aortic stenosis, and a ventricular septal defect the left ventricle was only moderately hypoplastic.

The pulmonary valve annulus, main pulmonary artery, and branch pulmonary arteries were invariably enlarged. All patients had a three-leaflet pulmonary valve. A left-sided patent ductus arteriosus supplied the descending aorta. A preductal coarctation ridge above the insertion of the patent ductus arteriosus was clearly seen in 8 patients. The long axial oblique sweep detected leftward deviation of the superior attachment of the septum primum in 8 patients. The atrial communication appeared to be adequate in 11 patients. One patient clearly had a very restrictive atrial defect.

The right ventricle was invariably enlarged and dilated. The tricuspid valve appeared to be morphologically normal in 11 patients and "mitralized" in 1 patient. Pulsed Doppler examination revealed a competent tricuspid valve in 5 patients, mild to moderate tricuspid regurgitation (TR) in 5 patients, and severe TR in 2 patients (Table 1). The right ventricular function was judged to be good in 4 patients, borderline in 5 patients, and clearly diminished in 3 patients. The 2 patients with severe TR had borderline or poor right ventricular function. Preoperative cardiac catheterization was not performed in any patient because of the accuracy of cardiac ultrasound and our belief that it may even be counterproductive because of the added stress on an already severely compromised newborn.

Preoperative Management

Perinatal survival of neonates with HLHS is dependent on maintenance of the systemic circulation through a patent ductus arteriosus. When the ductus starts to close, there is a progressive deterioration in systemic perfusion, leading to tissue hypoxemia and severe metabolic acidosis. Some degree of metabolic acidosis was seen in all neonates, but it was severe in 4 patients. Sufficient sodium bicarbonate was given to fully correct the metabolic acidosis. Although the mean arterial pressure was often normal, maintained by intense peripheral vasoconstriction, the perfusion of the kidneys, liver, and gut was often suboptimal. Oliguria with a rising serum creatinine level was present in 5 patients. Elevated liver function tests (2 patients), seizures (2 patients), and disseminated intravascular coagulopathy (1 patient) were seen in neonates in severe distress.

Constant infusion of prostaglandin E_1 through a peripheral or central venous line in an initial of dose of 0.05 to 0.1 μg/kg/min inhibited physiological closure of the patent ductus arteriosus in all neonates. After prostaglandin infusion, there was usually a dramatic increase in the arterial pH over hours and a dramatic decrease in the serum creatinine level over several days. Adequate fluids were always administered to maintain good urinary output. Diuretics were often given to stimulate urine production. Over several days, hepatic and gut function returned to normal. Arterial blood gases followed quite predictably the clinical status of the infant at the time. Because of apnea, a common side effect of prostaglandin infusion, all neonates were electively intubated and maintained on mechanical ventilation.

Because blood ejected from the right ventricle can pass through either the pulmonary circuit or the systemic circuit, careful management of the balance of pulmonary to systemic vascular resistance is an important part of the preoperative rescusitation. High concentrations of inspired oxygen (FiO_2) and hyperventilation (arterial carbon dioxide tension [$PaCO_2$], 25 to 30 mm Hg) selectively decrease pulmonary vascular resistance while increasing systemic vascular resistance. The arterial oxygen tension [PaO_2] will be better, but at the expense of poor peripheral perfusion and metabolic acidosis. All infants were maintained on low FiO_2 (21% to 35%) to optimize the peripheral arterial oxygen saturation at 80% to 85%. The volume ventilator was adjusted to maintain a $PaCO_2$ between 38 and 45 mm Hg, or higher if pulmonary blood flow seemed much increased. One neonate with excessively low neonatal pulmonary vascular resistance did not respond well to ventilator or oxygen manipulations.

A continuous infusion of dopamine (1 to 4 μg/kg/min) was used in all neonates to improve myocardial function and enhance urinary output. An infusion of dobutamine (1 to 5 μg/kg/min) was added in 2 patients with poor right ventricular function. Caution should be taken in administering these inctropic drugs in excess of 5 to 7 μg/kg/min as increasing the systemic vascular resistance is usually counterproductive because it can increase pulmonary blood flow. Serial echocardiograms before operation revealed improved right ventricular function in 6 of the 8 patients with borderline or poor function, usually within 48 hours.

The condition of most infants (10 infants) was adequately optimized with this treatment protocol. A restrictive patent foramen ovale is usually not a problem; in fact, a small patent foramen ovale may be protective because pulmonary vascular resistance remains elevated so systemic blood flow remains high. However, 1 patient who developed serious pulmonary venous congestion (PaO_2, 23 to 27 mm Hg) from a very small patent foramen ovale did not respond well to aggressive therapy. Despite persistent poor right ventricular function, the hemodynamics in these 2 patients did stabilize. A tight coarctation or a very hypoplastic ascending aorta did not prevent preoperative resuscitation. All neonates then underwent elective operation between three and six days of age, except for 1 patient with persistent left lung collapse. After several therapeutic bronchoscopies, the child's left lung fully reexpanded and he underwent operation at 16 days of age.

Surgical Technique

Induction of general anesthesia was achieved with pancuronium bromide (0.1 mg/kg) and fentanyl citrate (25 μg/kg). The thymus gland was excised through a median sternotomy, exposing the hypoplastic ascending aorta and transverse aortic arch. Surface cooling was begun with a cooling blanket and ice bags packed around the head. The diminutive ascending aorta was dissected free from the dilated main pulmonary artery (MPA). The arterial cannula was inserted in the most proximal MPA. A single venous cannula was placed in the right atrial appendage. The right and left pulmonary arteries were occluded to ensure systemic perfusion through the ductus arteriosus. Cardiopulmonary bypass was instituted and core cooling begun. Deep hypothermic circulatory arrest greatly facilitated aortic arch reconstruction. During cooling the aortic arch branches were dissected and looped with suture tourniquets. The transverse aortic arch down to the descending aorta and the patent ductus arteriosus were also dissected out. The patient was cooled to a rectal temperature of 18°C and a tympanic temperature of 15°C. Cardiopulmonary bypass was discontinued and the tourniquets on the head vessels were tightened. Cardioplegia was not given. The arterial and venous cannulas were removed. The atrial septum, which was often thick with a small patent foramen ovale, was completely excised through the right atrial appendage pursestring suture.

In an autopsy series, 55% of the patients had posterior leftward displacement of the superior attachment of the septum primum [17]. Appreciation of this unusual attachment was important to ensure wide excision of the septum primum to avoid late pulmonary venous obstruction. A left superior vena cava with a dilated coronary sinus (2 patients) further displaced the fossa ovalis superiorly. The ductus arteriosus was ligated at the pulmonary artery bifurcation and completely excised distally down to its entrance into the thoracic aorta. All ductal tissue was removed from the thoracic aorta to prevent late coarctation. The MPA was transected adjacent to the origin of the right pulmonary artery (Fig 1). The distal stump was closed with an aortic homograft patch to which a 4-mm polytetrafluoroethylene shunt had been anastomosed before circulatory arrest. Patch closure of the pulmonary artery bifurcation was performed to avoid loss of continuity between the right and left pulmonary artery branches, which has been occasionally observed when the distal stump was closed primarily with suture [18].

Although Bharati and Lev's [19] recent pathological study suggested a low incidence of serious coarctation with HLHS, most reviews report an incidence of about 70% to 80%, particularly when one includes the shelf of

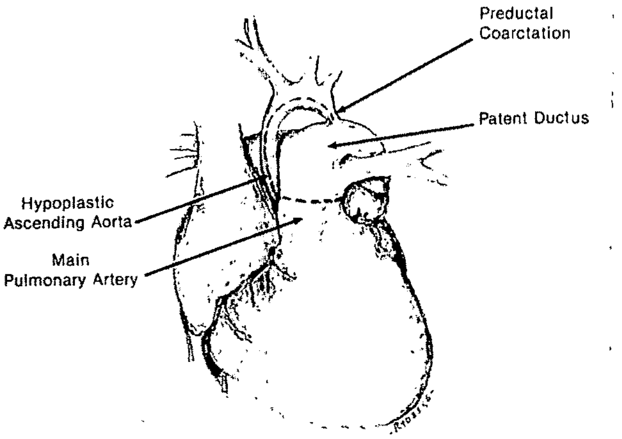

Fig 1. The external anatomy of hypoplastic left heart syndrome. The dotted lines *show the level for transection of the main pulmonary artery adjacent to the right pulmonary artery and the extensive aortotomy for aortic arch reconstruction.*

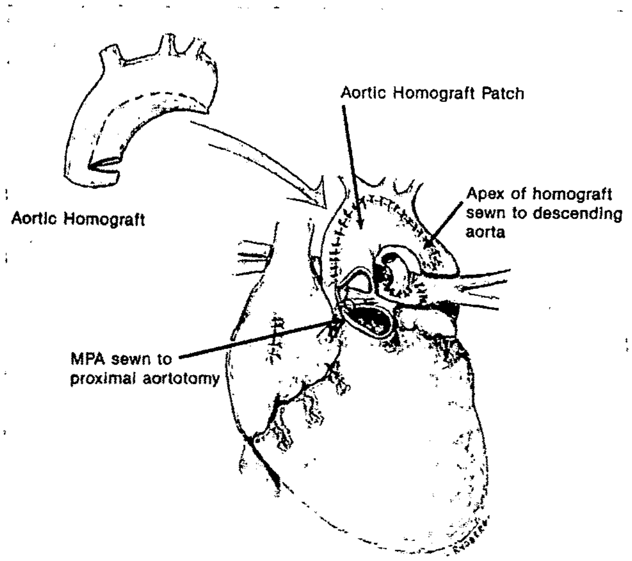
Aortic Homograft Patch
Aortic Homograft
Apex of homograft sewn to descending aorta
MPA sewn to proximal aortotomy

Fig 3. An aortic homograft augmentation patch (insert) is anastomosed to the descending aorta, hypoplastic transverse aortic arch, and hypoplastic ascending aorta. The main pulmonary artery (MPA) *is sewn to the proximal extent of the aortotomy.*

ductlike tissue found opposite the ductus arteriosus. Even if this tissue has no preoperative hemodynamic effect, it has the potential to cause late hemodynamic effects if not adequately dealt with at the time of stage I palliation. An incision in the aorta was carried distally about 2 cm beyond the junction of the ductus and descending aorta. The aortotomy was then extended proximally across the transverse aortic arch and down the ascending aorta to the level of the transected MPA (Fig 2). A cuff of aortic homograft was used for aortic arch augmentation because it is more hemostatic and pliable than synthetic alternatives (Fig 3). The proximal MPA was anastomosed to the proximal extent of the ascending aortotomy. Minimal distortion of this anastomosis can result in poor coronary perfusion. The aortic homograft patch was interposed between the hypoplastic ascending aorta–transverse aortic arch incision and the proximal descending aorta, and then finally anastomosed to the proximal MPA segment (Fig 4). Before the completion of the anterior half of the MPA anastomosis, the 4-mm shunt was anastomosed to the aortic homograft gusset about 5 mm beyond the posterior suture line. The central shunt was kept as short as possible. Cardiopulmonary bypass was reinstituted and the patient was rewarmed. The tourniquets on the aortic arch vessels were removed, but those on the branch pulmonary arteries remained until the patient was weaned from bypass. A central 4-mm shunt as described was constructed in the last 7 patients. In the first 5 patients, a 4-mm shunt was interposed between the right

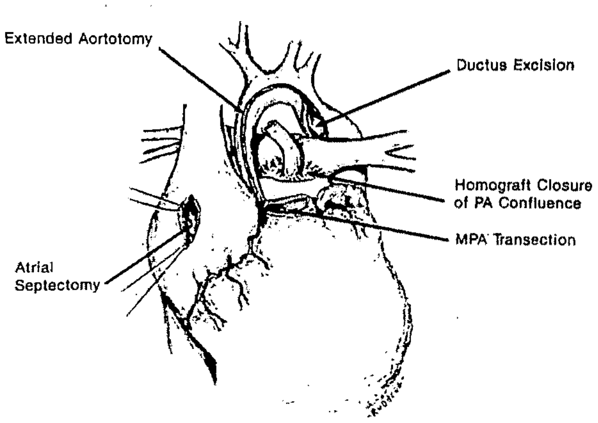

Fig 2. The distal pulmonary artery (PA) confluence is closed with an aortic homograft patch to which a 4-mm shunt has been anastomosed. The patent ductus arteriosus is ligated and excised down to the descending aorta. The aortotomy is begun 1 to 2 cm below the ductus arteriosus insertion and continued to the level of the proximal main pulmonary artery (MPA).

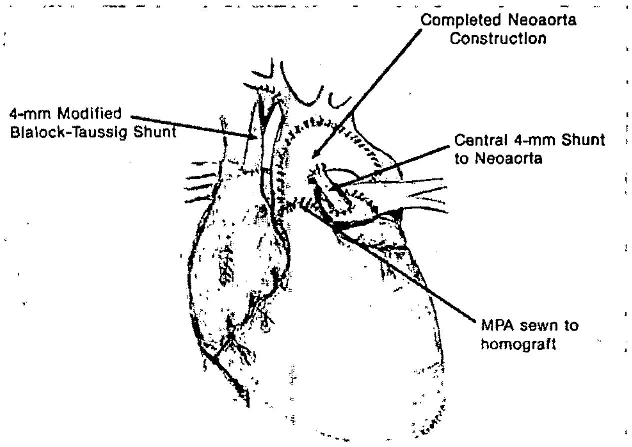
Completed Neoaorta Construction
4-mm Modified Blalock-Taussig Shunt
Central 4-mm Shunt to Neoaorta
MPA sewn to homograft

Fig 4. The aortic augmentation patch is sewn to the proximal main pulmonary artery (MPA). *A central 4-mm polytetrafluoroethylene shunt is interposed between the pulmonary artery confluence patch and the neoaorta. Alternatively, a 4-mm shunt can be interposed between the right innominate artery and the right pulmonary arter*

innominate artery and the right pulmonary artery after cardiopulmonary bypass was reinstituted.

Postoperative Management

The key to success in the early postoperative management is obtaining a critical balance between systemic and pulmonary vascular resistance. Shunt flow (that is, pulmonary blood flow) rises when the systemic vascular resistance increases or the pulmonary vascular resistance decreases. Shunt flow declines when the systemic vascular resistance decreases or the pulmonary vascular resistance increases. Generally pulmonary blood flow is low initially. Using the lowest possible mean airway pressure, hyperventilation ($PaCO_2$, 20 to 30 mm Hg), and a high FiO_2, the pulmonary vascular resistance usually falls and the PaO_2 rises to about 40 to 45 mm Hg. The majority of infants with aortic atresia have a restrictive interatrial communication, resulting in high pulmonary vascular tone which takes time to decrease after the atrial septectomy.

Inotropic support was utilized coming off bypass in all patients to maintain a systolic arterial pressure of 65 to 75 mm Hg and a peripheral arterial saturation of 75% to 80%. Continuous infusions of epinephrine (0.05 to 0.15 μg/kg/min) and norepinephrine (0.05 μg/kg/min) were initially used in 9 patients, whereas only epinephrine was used in 3 patients. Over time the norepinephrine (one hour to three days) and epinephrine (one hour to six days) infusions were weaned, as the hemodynamics stabilized. A continuous infusion of dopamine (1 to 4 μg/kg/min) was added in 5 patients to improve myocardial function and urinary output. As the pulmonary vascular resistance fell and the myocardial function improved, the peripheral arterial oxygen saturations stabilized at 82% to 86% on 21% FiO_2.

In the presence of an adequate systemic perfusion pressure (65 to 70 mm Hg systolic), a persistently low PaO_2 (less than 25 mm Hg) usually implies an inadequate shunt and will quickly result in myocardial failure, systemic hypotension, and worsening hypoxia if not corrected. This problem was not seen in this small series. A PaO_2 greater than 50 mm Hg, persistent metabolic acidosis, and systemic hypotension usually suggest large pulmonary blood flow and inadequate systemic perfusion. Children with this condition are prone to very sudden cardiac arrest. Subsequent resuscitation is almost impossible. One should attempt to maximize pulmonary vascular resistance and minimize systemic vascular resistance. The neonate should be ventilated with an FiO_2 of 21% and the $PaCO_2$ should be maintained between 45 and 50 mm Hg. Metabolic acidosis should be aggressively treated. Despite hypotension, the use of high doses of vasopressors can increase systemic vascular resistance and increase shunt perfusion pressure. Persistently high shunt flow, despite these manipulations, should suggest the possibility of a residual aortic obstruction or an excessively large shunt.

The surviving neonates were slowly weaned from the ventilator (two to 28 days). Central hyperalimentation was usually started on the third postoperative day. Nasogastric feedings were begun as soon as the ileus resolved. Administration of digoxin and diuretic agents was routinely begun on the second postoperative day to manage mild congestive heart failure.

Results

Two patients died shortly after operation. One patient with excessively low pulmonary vascular resistance before operation, poor right ventricular function, and severe tricuspid insufficiency arrested within one hour. Ongoing low cardiac output and persistent metabolic acidosis in another patient with borderline right ventricular function and severe TR did not respond to aggressive therapy and led to death within eight hours. Ten neonates survived operation with aggressive postoperative management. Six of 8 patients with preoperative borderline or poor right ventricular (RV) function survived, whereas all 4 patients with good RV function survived. Both patients with severe TR died.

Systemic sepsis developed in 3 patients and responded well to a brief course of antibiotics and removal of intracardiac catheters. One patient had three cardiac arrests associated with alterations in ventilation with sudden increases in $PaCO_2$ and acidosis. Each time his sternotomy incision was opened and closed later (24 hours), and yet he ultimately survived. Feeding problems were common (6 patients), often delaying discharge several weeks until the child could take his or her entire diet by mouth. At discharge, chest roentgenograms showed mild to moderate cardiomegaly and fairly normal pulmonary vascular markings. Serial electrocardiograms demonstrated sinus rhythm in all children. Follow-up echocardiograms revealed patent aortopulmonary shunts, no neoaortic valve insufficiency, and no early residual aortic obstructions. The 4 patients with good preoperative RV function continued with excellent function (Fig 5). Of the 4 surviving patients with borderline function, 2 patients had good function late and 2 continued with borderline function. The 2 surviving patients with poor RV function before operation had either good (1) or borderline (1) function at late follow-up. The 5 patients without TR before operation continued without TR (Fig 6). Moderate TR improved after operation in 2 patients and remained the same in 3 patients.

All patients have been followed closely by a pediatric cardiologist. Administration of digoxin and diuretic

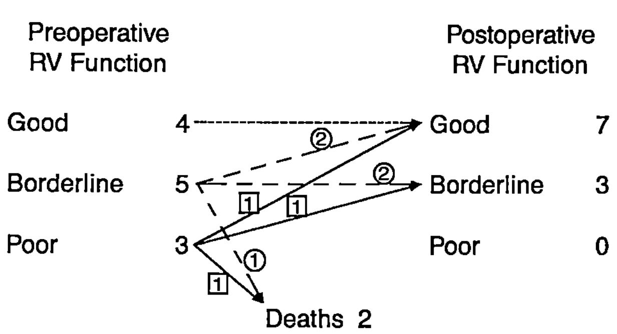

Fig 5. Comparison of right ventricular (RV) function before and after stage I palliation.

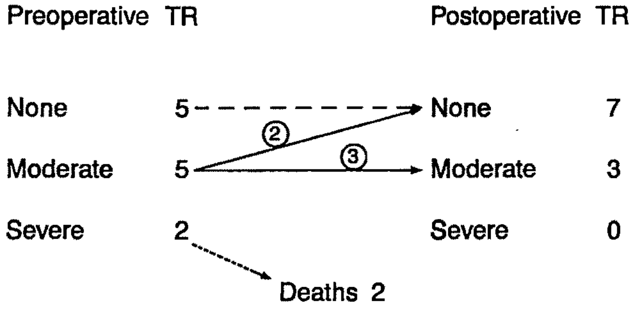

Fig 6. Comparison of the degree of tricuspid regurgitation (TR) before and after stage I palliation.

agents has been continued in all children. All patients remain in sinus rhythm. Late chest roentgenograms revealed some increase in heart size in 2 patients. The late peripheral arterial oxygen saturations range from 72% to 78%. Serial clinical examinations, confirmed by echocardiography, have not revealed any late aortic obstructions. The hemoglobin concentration rose over follow-up to 17 to 19 g/100 mL. Two late deaths have occurred. One patient died 7 months after operation from a resistant staphylococcal pneumonia and 1 died 13 months later from suspected hypoxemia. One patient had a second aortopulmonary shunt at 15 months of age for progressive polycythemia. The 8 surviving patients await stage II physiological correction.

Comment

Over time, the operative mortality of stage I palliation has decreased with increased surgical experience and particular attention to the rapidly changing pulmonary vascular bed. Table 2 summarizes several recent series, detailing early and late deaths after stage I palliation. The early mortality (17%) in this small series compares quite favorably with that of other large series. The majority of early deaths in these series were related to technical difficulties in the perioperative period [7]. Severe TR (2 patients), a very restrictive atrial defect (1 patient), and very low pulmonary vascular resistance (1 patient) contributed to the 2 early deaths in this series.

The shocklike state that occurs before the institution of prostaglandins may produce serious physiological and pathological changes that may limit the outcome after surgical palliation. Coronary perfusion may be compromised by a closing ductus arteriosus. High pulmonary vascular resistance after birth together with a closing ductus arteriosus imposes a postnatal load on the right ventricle, increasing myocardial oxygen "demand." Thus, hemodynamic changes during transition to extrauterine life affect myocardial oxygen "supply and demand," and may well contribute to early myocardial dysfunction.

Lloyd and colleagues [22] studied the right ventricle in 51 cases of untreated HLHS. The most striking finding was extensive subendocardial necrosis and occasional areas of transmural infarction. The lack of notable fibrosis or endocardial fibroelastosis argued against long-standing antenatal insult to the myocardium. The degree of RV preservation was independent of the size of the ascending aorta. The histological features of myocardial necrosis were consistent with postnatal occurrence of infarction, suggesting that early vigorous supportive care in infants with HLHS may preserve myocardial function. Occasionally, however, extensive necrosis of the right ventricle was present in infants who died on the first day of life, indicating that a few infants may have irreversible RV dysfunction before surgical palliation is attempted.

When first seen, infants with HLHS frequently have regional wall motion abnormalities and depressed RV ejection fraction noted on two-dimensional echocardiography [23, 24]. Bash and associates [25] observed by serial echocardiography that RV function frequently normalized over several days after administration of prostaglandins was started. In this series, 10 of the 12 patients had some improvement in their preoperative RV function before operation with the aggressive preoperative protocol outlined. Additionally, 4 of 8 patients (50%) with borderline or poor RV function before operation had much improved function after palliation, implying that some of the early RV dysfunction was reversible. Certainly poor RV function is not a contraindication to stage I palliation, although the outcome may not be as satisfactory.

The tricuspid valve is usually structurally normal, although TR is often detected by echocardiography. Pre-

Table 2. Overview of Results of Stage I Palliation of Hypoplastic Left Heart Syndrome

Author	Year	Total Number	Early Deaths	Late Deaths	Survivors
Norwood et al [7]	1981	16	8	3	5 (31%)
Moodie et al [20]	1986	10	6	1	3 (30%)
Jonas et al [16]	1986	25	6 (24%)	4	15 (68%)
HLHS Symposium [21]	1986	249	174 (70%)	. . .	. . .
Centers <16 patients		111	101 (91%)	. . .	. . .
Centers >35 patients		138	73 (53%)	. . .	. . .
Pigott et al [15]	1988	104	30 (29%)	11	63 (60%)
Gustafson et al [present report]	1989	12	2 (17%)	2	8 (66%)

HLHS = hypoplastic left heart syndrome.

operatively, 7 patients (58%) in this series had clinically significant TR, which disappeared in 2 patients. In 25% of the survivors in the study by Pigott and co-workers [15], the TR also improved after palliation. The tricuspid insufficiency must at least in part be related to preoperative ventricular dysfunction. In this small series, patients with mild to moderate TR did as well as those without TR. Both our patients with severe TR died, though they also had diminished RV function.

Early palliative procedures using conduits from the right ventricle or pulmonary artery to the descending aorta did not take into account the frequent preductal coarctation flange, which might limit retrograde coronary blood flow. Direct anastomosis of the MPA to the transverse arch is not possible if one is to deal adequately with the coarctation and prevent distortion from excessive tension. A conduit with a long distal bevel can be interposed between the MPA and the undersurface of the transverse arch, but with the obvious disadvantages of leaving a "single" coronary artery system and requiring conduit replacement with growth [16]. The right ventricle will not tolerate residual outflow tract obstruction perioperatively. Failure to deal with the coarctation will be reflected in systemic hypotension, high PaO_2 (greater than 50 mm Hg), and persistent metabolic acidosis, analogous to ductal closure preoperatively.

Routine extension of the aortic augmentation distal to the ductus insertion was done to minimize the potential for obstruction at the site of the posterior juxtaductal ridge. The aortic homograft patch is more pliable and hemostatic than synthetic alternatives and "molds" into place much easier. Postoperative hemorrhage from the long suture lines was not a problem. The internal diameter of the hypoplastic ascending aorta in this series did not correlate with early outcome, suggesting that even a very small ascending aorta can be anastomosed to the proximal MPA and the augmentation patch without coronary insufficiency. Neoaorta reconstruction with an aortic homograft patch could conceivably distort the native aortic root, although this has not been observed in postoperative autopsy studies [17]. Late follow-up angiograms have demonstrated excellent growth of the aortic root and the coronary arteries when a homograft gusset was used [16]. However, despite routine homograft augmentation, Pigott and colleagues [15] found 11 (20%) late aortic arch obstructions in survivors of stage I palliation, which were all treated surgically. To date, no aortic obstructions have been identified over follow-up in this series.

Because blood ejected from the single right ventricle can pass into either the pulmonary or systemic circulation, the size of the aortopulmonary shunt is critical, particularly in the early postoperative period when the pulmonary vascular resistance is extremely dynamic. In the first 5 patients, a 4-mm polytetrafluoroethylene graft was interposed between the right innominate artery and the right pulmonary artery. After relative hypoplasia of the left pulmonary artery was recognized in some series after this type of shunt [15], we switched to interposing a 4-mm graft from the neoaorta to the pulmonary artery confluence to promote more symmetrical growth of the right and left pulmonary arteries. A 3-mm modified right Blalock-Taussig shunt usually affords too little pulmonary blood flow, whereas a 5-mm shunt often results in massive pulmonary flow.

The pulmonary artery bifurcation was closed with an aortic homograft patch to minimize late proximal stenosis of the branch pulmonary arteries. Despite the routine use of such a patch, Weinberg and colleagues [17] found severe distortion of the midportion of the pulmonary artery confluence in some late deaths after stage I palliation. It is possible that there is residual ductal tissue that gradually constricts, resulting in such deformities. We hope that, by inserting the central shunt into the homograft patch used to close the pulmonary artery confluence, the incidence of branch stenosis can be farther reduced.

For a child to be a suitable candidate for a stage II Fontan procedure, RV function must be preserved, the atrial septal defect must be nonrestrictive, the pulmonary vascular resistance must be low, the neoaorta must be unobstructed, and the pulmonary artery bifurcation must be minimally distorted. Lang and Norwood [13] studied 10 patients after stage I palliation and found that if the aortic reconstruction was unobstructed and pulmonary blood flow was balanced and limited, RV function was usually preserved. The good RV function in 8 of our survivors is encouraging. These children, although cyanotic, are an appropriate height and weight for their age, and the majority are developmentally normal.

Still, late deaths before stage II palliation continue to be a problem in all reported series [15, 16]. The 2 late deaths in our series are disturbing. The long-term fate of the right ventricle as the systemic ventricle will be known only as more patients survive stage II. The efficacy of this multistaged approach to HLHS must therefore await long-term follow-up of a substantial group of patients.

In summary, HLHS is a prevalent cardiac malformation that is uniformly fatal without surgical intervention. Any systemic approach aimed at improving long-term survival of these neonates demands an early diagnosis by two-dimensional echocardiography, immediate institution of prostaglandins, and careful attention to preoperative care. The ability to optimize the hemodynamic and metabolic condition of most infants has made surgical palliation a realistic option for this otherwise lethal lesion. The expanded application of the Fontan procedure to many previously uncorrectable cardiac defects has prompted increasing interest in surgical palliation. Because of high neonatal pulmonary vascular resistance, a staged surgical approach is necessary. This series and other current surgical series, particularly those of Norwood and associates, suggest that the natural history of HLHS can be substantially altered by a reconstructive operation. Modifications in the technique of initial palliation, like those described in this series, are constantly occurring to minimize late complications that might make a second stage procedure more treacherous. With more experience, the surgical results will continue to improve. Alternatively, cardiac allotransplantation could prove to be a viable alternative. However, the availability of potential neonatal donors is presently very limited.

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Incidence of Cell-Saver Contamination During Cardiopulmonary Bypass

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During regular bacteriological surveillance of cardiac surgical equipment and patients, the Cell Saver apparatus (CSA) was prospectively evaluated to determine if it represented an additional risk for infection. Nineteen patients were studied. After each operation, the effluent from the CSA was sterilely sealed for subsequent culture. A total of 42 aerobic and 42 anaerobic cultures were made. Postoperatively all patients were evaluated daily for four days and before discharge for clinical evidence of infection. Four patients had positive CSA cultures without evidence of postoperative clinical infection. Five patients in whom postoperative infectious complications developed had negative CSA cultures. Ten patients had negative CSA cultures and no evidence of postoperative infection. We conclude that the CSA does not appear to contribute to the risk of infection in cardiac surgical patients and that it is a safe adjunct to cardiac surgery.

(Ann Thorac Surg 1989;48:51–3)

Infection is a major cause of morbidity and mortality in cardiac surgical patients. Regular bacteriological surveillance of all apparatus used to treat patients undergoing cardiopulmonary bypass (CPB) is necessary to ensure that the patients are not exposed to additional risk of infection. Surveillance of personnel and equipment used in the operating room has been reported [1]. Operating room personnel and both anesthesia and surgical equipment have been implicated as a cause of postoperative sepsis [2, 3]. The heart-lung machine [4], coronary suction system [5], intravenous and urinary catheters, and endotracheal tubes [1, 6, 7] have all been described as sources of infection. The importance of such cultures is not entirely clear, as positive blood cultures from apparatus have not always been associated with clinical infection in patients [4]. Comparable information about the Cell Saver apparatus (CSA) is not available because the CSA has not been so studied.

The CSA provides autologous blood for reinfusion, and was introduced amid growing concern over the increasing use of blood and its components during surgical procedures requiring cardiopulmonary bypass. The National Institutes of Health recommended increased use of autologous blood transfusions in 1973 [8]. More recently, concerns over blood-borne infections such as hepatitis, cytomegalovirus, and acquired immunodeficiency syndrome have emphasized the need to minimize exposure to heterologous transfusion.

The purpose of this study was to prospectively evaluate the incidence of CSA contamination and its possible contribution to postoperative infection.

Material and Methods

The CSA (Haemonetics Cell Saver, Haemonetics Corp, Braintree, MA) is a centrifuge that, when simultaneously spinning and washing its contents with saline solution, leaves in its bowl the heavy elements of the blood suctioned from the field (ie, the cells). The CSA removes the lighter elements, the proteins, and the saline washings, transferring all of the latter to a waste bag. With continuing centrifugation, the erythrocytes gradually fill the CSA bowl. When it is filled, the cells are washed with saline solution and transferred to a reinfusion bag for return to the patient. All parts of the CSA that come into contact with blood are disposable.

The CSA to be studied was selected at random from procedures in which bypass times were expected to be of at least average duration. Cultures were obtained, and patients were followed postoperatively and checked for the development of infectious complications.

The waste bag from the CSA was sterilely sealed at the conclusion of the operation and sent intact to the Clinical Microbiology Laboratory. There, under sterile conditions, 50 mL of the washings was transferred from the waste bag to a sterile 50-mL plastic centrifuge tube and spun at 2,000 rpm for ten minutes, producing a sediment that was then used to inoculate one sheep blood agar plate, one chocolate agar plate, one MacConkey agar plate, and one vial of thioglycolate broth. The sheep blood and chocolate plates were inoculated at 35°C in the presence of carbon dioxide; the MacConkey plate and the thioglycolate broth were incubated aerobically at 35°C. These inoculates were examined for growth daily for four days.

Infection in the patients was defined as the presence of usual signs and symptoms, namely, oral temperature greater than 38.5°C, cough productive of purulent sputum, clinical evidence of urinary tract infection, findings suggestive of pneumonia on chest roentgenogram, and

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hemodynamic indices consistent with septic shock. Cultures were grown from blood, sputum, and urine specimens as indicated by the clinical pictures of infection.

Nineteen patients undergoing an elective cardiac operation requiring cardiopulmonary bypass and the use of the CSA were studied. Anesthesia practice included intravenous radial and pulmonary artery catheters placed under sterile conditions and routine administration of antibiotics before skin incision. The anesthesia techniques and support methods employed were at the discretion of the attending physicians. Use of the CSA was discontinued at the end of the surgical procedure, and it was not used postoperatively in the intensive care units.

Exact binomial p value for matched-pair 2 × 2 table (χ^2) was used for statistical analysis. A p value of less than 0.05 was considered significant.

Results

Nineteen patients (13 men, 6 women) aged 35 to 77 years, with a body surface area of 1.91 ± 0.23 m^2 (mean ± standard deviation), were entered into the study. Fifteen underwent coronary artery bypass grafting (one of these a repeat procedure), 2 had aortic valve replacement (one of these a repeat procedure), 1 had repeat mitral valve replacement, and 1 underwent combined coronary artery bypass grafting and aortic valve replacement. The operations lasted 309 ± 88 minutes, and the length of cardiopulmonary bypass was 128 ± 34 minutes. The CSA was in use for the duration of the operation with suction pressures of 120 mm Hg.

All patients received prophylactic antibiotics: 17 patients received 1.0 g of cefazolin sodium and 2 patients, 1.0 g of vancomycin. Two to 12 units (mean amount, 4.5 ± 2.4 units) of autologous blood from the CSA was transfused to each patient.

A total of 21 bags of effluent from the CSA were sent for culture, one bag from each of 17 patients and two bags from each of 2 patients. As two aerobic and two anaerobic cultures were grown from each bag, a total of 42 aerobic and 42 anaerobic cultures were studied.

Three of the 42 anaerobic cultures were positive for diphtheroids, and one of the 42 aerobic cultures was positive for *Staphylococcus epidermidis*. None of the 4 patients with positive cultures of the CSA waste bag had infectious complications during the hospital stay.

In 5 of the remaining 15 patients, infectious complications developed during hospitalization. Three of these patients had lower respiratory infections manifested clinically by a productive purulent cough. Cultures of sputum from 1 patient grew *Klebsiella*, and from the other 2 patients, normal oral flora. These episodes resolved, and the patients were discharged with no sequelae. One patient sustained a stroke and required prolonged ventilatory support; *Candida albicans* pneumonia developed. One patient, whose sternum was kept open because of poor ventricular performance, died in septic shock on the third postoperative day. Though clinical measurements indicated septic shock, blood cultures remained negative. None of these 5 patients in whom clinical signs of infection developed had positive cultures from the CSA.

Statistical analysis revealed no significant correlation between the use of the CSA and the incidence of postoperative infection.

Comment

Cardiac surgical patients are prone to experience septic complications [9–21]. In addition to postoperative hemorrhage with formation of mediastinal hematoma, prolonged operative time, sternotomy itself [11], debilitated status of some patients [2, 12], and invasive monitors and catheters [1, 6, 13], cardiopulmonary bypass involves exposure of blood to foreign surfaces and is associated with perioperative impairment of both cellular and humoral components of host defenses [9–11, 13–15]. This continues to be true despite many improvements in apparatus design and operative techniques. A recent study [15] demonstrated severe dysregulation of the immune system not found in patients undergoing general surgical procedures without bypass.

The relationship between apparatus cultures and patient infection may be obscured by the antibiotic prophylaxis that is almost universal even though the data to support such practice is scarce [19–21]. First-generation cephalosporins such as cefazolin have been widely used for such prophylaxis and may be preferable to second- or third-generation cephalosporins in terms of effectiveness, cost, and range of activity. Because of its longer half-life, cefazolin (the cephalosporin used in this study) is the first-generation cephalosporin of choice. Although much variability exists regarding the dosage and duration of the prophylactic therapy, the regimen used in this study represents common practice. The effect of antibiotic prophylaxis on cultures from the apparatus and their relationship to infection in the patients is, as in other studies, unclear.

Infections from the surgical environment and apparatus used for open heart operations have been extensively studied and reviewed [4, 5, 7, 20, 21]. A study of the heart-lung machine [4] showed that 16 (2.4%) of 657 blood cultures from the machine itself were positive for bacteria. Twelve of these 16 patients demonstrated absence of clinical infection. Three of the remaining 4 patients were already infected and thus contaminated the heart-lung machine. In only 1 patient was the cause of infection the heart-lung machine itself; ie, positive cultures in the apparatus correlated poorly with infection. Thus, the heart-lung machine did not appear to add a major risk of infection.

Intraoperative autotransfusion is not a new idea. Highmore [22] first suggested its use in 1874. The expense involved, the fears of coagulopathy, and the perceived safety of the blood supply hindered early acceptance. More recently, concerns about the blood supply, particularly with respect to acquired immunodeficiency syndrome, have led to a renewed interest in intraoperative autotransfusion [23, 24].

A number of autotransfusion devices are commercially available. In general, blood is collected, filtered, and then either reinfused directly or washed and then reinfused. The apparatus used in our study reinfused washed cells.

Washing the blood cells with sterile saline solution does not ensure that the reinfusate is uncontaminated. However, our study showed that none of the patients with positive inoculates experienced infectious complications and that none of the patients with postoperative infectious complications had positive inoculates. This finding is analogous to that seen with the heart-lung machine (ie, positive cultures did not always mean patient infection).

Nevertheless, despite the many new antibiotics that have been developed, techniques such as host defense enhancement [25], and refinements in apparatus design, bacteriological surveillance of equipment and patients remains important in the evaluation of postoperative infection.

In conclusion, this study demonstrated the presence of positive blood cultures from an apparatus (the CSA) that is widely used and in direct contact with the patient's blood during an open heart operation. It also showed, however, that these cultures did not correlate with clinical infection in the patient. The CSA thus appears a safe adjunct to open heart operations.

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A 10-Year Comparison of Mitral Valve Replacement With Carpentier-Edwards and Hancock Porcine Bioprostheses

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Two hundred fifty-three patients who underwent isolated mitral valve replacement with a porcine bioprosthesis had long-term evaluation. One hundred forty-seven patients received a Carpentier-Edwards porcine bioprosthesis and 106, a Hancock valve. There were no significant differences in preoperative clinical characteristics between the two groups. Cumulative follow-up was 1,375 patient-years. At 10 years, 93% ± 2.5% of the patients in the Carpentier-Edwards group and 85% ± 7.8% of those in the Hancock group were free from valve-related death (not significant), and 95% ± 2% and 91% ± 3.8%, respectively, were free from thromboembolism (not significant). At 10 years, 65% ± 7.2% of the patients in the Carpentier-Edwards group and 66% ± 7.2% of those in the Hancock group were free from structural valve deterioration (not significant), and 64% ± 6% and 59% ± 7.3%, respectively, were free from reoperation (not significant). We conclude that the first generation of Carpentier-Edwards and Hancock prostheses produce comparable long-term results in the mitral position.

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Porcine bioprostheses treated with glutaraldehyde have been used for mitral and aortic valve replacement since 1968 [1]. However, only since 1974 has the bioprosthetic valve been commercially available and widely implanted. The Carpentier-Edwards prosthesis and the Hancock prosthesis have been the most frequently used porcine bioprostheses. They differ somewhat in the glutaraldehyde concentration and the type of supporting stent.

During the period January 1975 to December 1979, both types of porcine bioprostheses were commonly used in our institution without special selection or randomization; the choice depended mainly on the preference of the individual surgeon. The aim of this study was to compare long-term performance characteristics of Hancock or Carpentier-Edwards porcine mitral bioprostheses implanted in the same institution by the same team and over the same period.

Material and Methods

Two hundred fifty-three patients who underwent isolated mitral valve replacement with a porcine bioprosthesis between January 1975 and December 1979 constitute the material of this study. They were separated into two groups based on the type of valve implanted: 147 patients received a Carpentier-Edwards valve and 106, a Hancock valve. Age ranged from 18 to 77 years (mean age, 53.6 ± 11.3 years and 50.2 ± 13.3 years, respectively).

Analysis of multiple preoperative variables—mean age, proportion of patients aged less than and more than 35 and 55 years, mean preoperative functional class, mean cardiothoracic ratio, incidence of atrial fibrillation, mitral valve lesion, and etiology—did not show any significant differences between the two cohorts (Table 1).

Information on operative mortality and complications was collected as part of the follow-up. Long-term follow-up was completed over a 4-month interval (January through April 1987) through questionnaires and telephone contacts with patients and their referring physicians. The average duration of follow-up of surviving patients was 7.2 ± 2.3 years for the Carpentier-Edwards group and 6.8 ± 2.9 years for the Hancock group (range, 7 to 12 years). The cumulative follow-up was 826 patient-years for the Carpentier-Edwards group and 549 patient-years for the Hancock group.

Postoperative Anticoagulation

All patients received immediate postoperative anticoagulant therapy with subcutaneous administration of heparin sodium beginning six hours after operation and continuing for ten days thereafter. Oral anticoagulation with warfarin sodium was initiated at that time and was eventually discontinued after 3 months depending on the decision of the referring cardiologist, rather than that of the surgeon, provided the patient was in sinus rhythm. Seventy-five percent of the surviving patients in both groups are on a regimen of long-term anticoagulation.

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Table 1. Preoperative Clinical Characteristics of the Two Patient Groups[a–c]

Variable	Carpentier-Edwards (n = 147)	Hancock (n = 106)
Age		
Mean (yr)	53.6 ± 11.3	50.2 ± 13.3
Patients <35 yr	8	7
Patients >35 yr	139	99
Patients <55 yr	76	56
Patients >55 yr	71	50
Preoperative functional class	2.6 ± 0.7	2.5 ± 0.6
Preoperative cardiothoracic ratio	0.6 ± 0.07	0.59 ± 0.06
Cardiac rhythm		
Sinus rhythm	52 (35)	13 (12)
Atrial fibrillation	95 (65)	93 (88)
Predominant functional lesion		
Mitral stenosis	27 (18)	17 (16)
Mitral regurgitation	48 (33)	30 (28)
Mixed mitral lesions	72 (49)	59 (56)
Etiology		
Rheumatic fever	103 (70)	80 (75)
Degenerative disease	37 (25)	22 (21)
Ischemic disease	3 (2)	3 (3)
Endocarditis	2 (1)	1 (1)
Previous prosthesis	2 (1)	0 (0)

[a] There were no significant differences between the two groups. [b] Where applicable, data are shown as the mean ± the standard deviation. [c] Numbers in parentheses are percentages.

Definitions

Stringent definitions for all valve-related complications derived from the Stanford framework were used in this study [2]. Structural valve deterioration was defined as an intrinsic abnormality of the prosthesis (leaflet disruption, calcification) causing stenosis or regurgitation found at autopsy or reoperation.

Table 2. Causes of Hospital Death[a]

Cause	Carpentier-Edwards (n = 147)	Hancock (n = 106)
Valve thrombosis	1	1
Cardiac failure	9	13
Myocardial infarction	0	1
Aortic dissection	1	0
Surgical hemorrhagic complication	2	1
Sudden death	0	1
Sepsis	0	2
Total	13 (8.8)	19 (17.9)

[a] Numbers in parentheses are percentages.

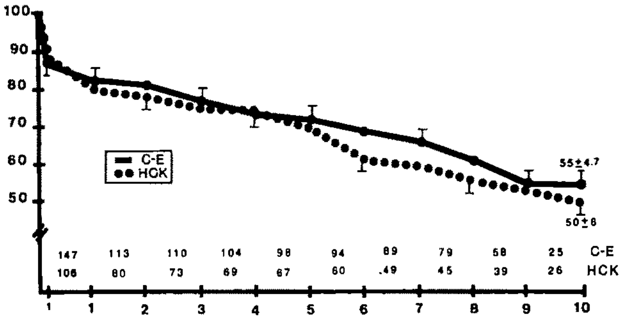

Fig 1. Actuarial survival curves. Operative mortality is included. (C-E = *Carpentier-Edwards;* HCK = *Hancock.)*

Thromboembolism was defined as the occurrence of any new focal neurological deficit, whether transient or permanent, unless it could be proved unequivocally to be due to another cause. Peripheral emboli were also included in this category unless the embolus clearly did not arise from the heart. This category also included valve thrombosis.

Anticoagulant-related hemorrhage included all episodes of internal or external bleeding resulting in hospitalization, transfusion, or death.

Reoperation included all valve reoperations regardless of the indication, including re-replacement and suturing of a periprosthetic leak.

Valve failure encompassed all valve-related complications prompting reoperation or causing death (structural valve deterioration, prosthetic valve endocarditis, periprosthetic leak, hemodynamic valvular dysfunction, thromboembolism, anticoagulant-related hemorrhage).

Valve-related death was defined as valve failure leading to death.

Statistical Analysis

Standard actuarial and linearized techniques were used to describe survival and the incidence of valve-related complications [3–5]. The log-rank test was used to compare actuarial curves [6]. Continuous data are presented as the mean ± the standard error of the mean.

Patients continued in the study until valve removal, death, or loss to follow-up. Patients were removed "alive"

Table 3. Causes of Late Death

Cause	Carpentier-Edwards (n = 147)	Hancock (n = 106)
Valve-related death	7	3
Cardiac-related death	12	9
Sudden death	9	8
Noncardiac		
Cancer	4	1
Other	3	3
Unknown	4	2
Total	39	26

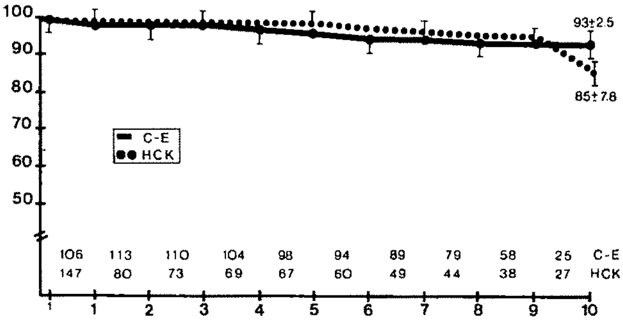

Fig 2. Actuarial curves of freedom from valve-related death. (C-E = *Carpentier-Edwards;* HCK = *Hancock.)*

from the study when the original valve was replaced or when an additional valve replacement was required.

Only the first event for each patient during the study was considered for the actuarial analysis, whereas all events for each patient were considered in the linear analysis.

Results

Operative Mortality

Thirty-day operative mortality was 8.8% in the Carpentier-Edwards group and 17.9% in the Hancock group. The causes of death are listed in Table 2. One of the early deaths in each group was valve related (valve thrombosis).

Late Survival

Long-term actuarial survival is shown in Figure 1. Ten-year survival rates were 55% ± 4.7% in the Carpentier-Edwards group and 50% ± 6% in the Hancock group. The difference between the two groups was not significant. The causes of late death were grouped into five different categories: valve-related death, cardiac-related death, sudden death, noncardiac cause, and unknown (Table 3).

Table 4. Summary of Linearized Rates of Valve-Related Complications[a,b]

Complication	Carpentier-Edwards (n = 147)	Hancock (n = 106)
Valve-related death	0.9 ± 0.3	0.9 ± 0.4
Thromboembolism	0.8 ± 0.3	1.1 ± 0.4
Structural valve deterioration	2.9 ± 0.5	2.6 ± 0.7
Reoperation	3.5 ± 0.6	4.1 ± 0.8
Valve failure	4.1 ± 0.7	4.1 ± 0.8
Anticoagulant-related hemorrhage	1 ± 0.3	1.3 ± 0.4
Valve-related mortality and morbidity	4.8 ± 0.7	5.6 ± 1.1

[a] Data are shown as percent per patient-year. [b] Data are shown as the mean ± the standard error of the mean.

Table 5. Causes of Valve-Related Death

Cause	Carpentier-Edwards (n = 147)	Hancock (n = 106)
Valvular thrombotic occlusion	2	1
Thromboembolism	0	0
Anticoagulant-related hemorrhage	4	0
Structural valve deterioration	1	3
Total	7	4

Valve-Related Deaths

At 10 years, 93% ± 2.5% of the patients in the Carpentier-Edwards group and 85% ± 7.8% of those in the Hancock group were free from valve-related death (Fig 2). Statistical analysis showed no significant difference between the two groups. The linearized rates were 0.9% ± 0.3% per patient-year for the Carpentier-Edwards group and 0.9% ± 0.4% per patient-year for the Hancock group (Table 4). The causes of valve-related death are listed in Table 5. Including sudden death in the causes of valve-related death, 83% ± 4.8% of the patients in the Carpentier-Edwards group and 76% ± 8.2% of those in the Hancock group were free from valve-related death. Again, no significant difference was seen between the two groups.

Thromboembolism

On an actuarial basis, 95% ± 2% of the patients in the Carpentier-Edwards group and 91% ± 3.8% of the patients in the Hancock group were free from thromboembolic complications at 10 years (Fig 3). The linearized rates were 0.8% ± 0.3% and 1.1% ± 0.4% per patient-year, respectively (see Table 4). Differences between the two groups were not significant. Two fatal episodes of thrombotic valvular occlusion occurred in the Carpentier-Edwards group and one in the Hancock group. The other thromboembolic complications in both groups were transient and regressive.

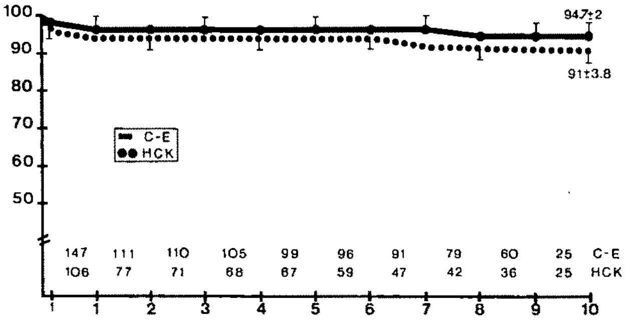

Fig 3. Actuarial curves of freedom from thromboembolism. (C-E = *Carpentier-Edwards;* HCK = *Hancock.)*

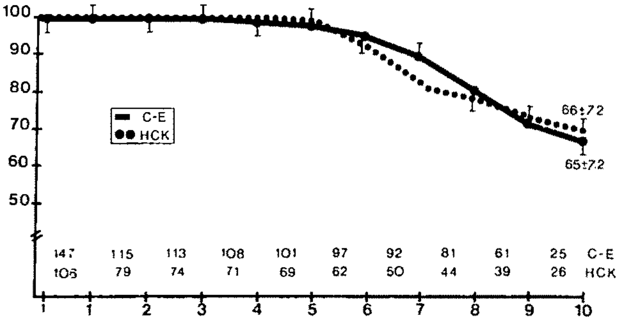

Fig 4. Actuarial representation of freedom from structural valve deterioration. (C-E = Carpentier-Edwards; HCK = Hancock.)

Table 6. Causes of Reoperation

Cause	Carpentier-Edwards (n = 147)	Hancock (n = 106)
Structural valve deterioration	24	14
Thrombosis	2	1
Periprosthetic leak	3	4
Endocarditis	0	3
Inadequate size	0	1
Total	29	23

Structural Valve Deterioration

At 10 years, 65% ± 7.2% of the patients in the Carpentier-Edwards group and 66% ± 7.2% of those in the Hancock group were free from structural valve deterioration (Fig 4). The difference was not significant. All of the patients with diagnosed structural valve deterioration were scheduled for an elective reoperation. Of the 24 patients with structural valve deterioration in the Carpentier-Edwards group and the 14 in the Hancock group who had reoperation, 1 (4%) in the Carpentier-Edwards group died (postoperative heart failure) and 3 (21%) in the Hancock group died (2 of mediastinitis and 1 of postoperative heart failure). Linearized rates are shown in Table 4. The prosthetic valves used at reoperation were as follows: 23 Starr-Edwards, 10 porcine bioprostheses, and 5 St. Jude Medical.

It is of note that in the Carpentier-Edwards group, four of the cases of structural valve deterioration occurred in the 8 patients younger than 35 years. In this same group, 16 cases occurred in the 76 patients younger than 55 years, and only eight cases were found in the 71 patients older than 55 years. The same situation prevailed in the Hancock group, with three cases of structural valve deterioration in the 7 patients younger than 35 years old. The 56 patients younger than 55 years experienced ten cases of structural valve deterioration, whereas the 50 patients older than 55 experienced four cases.

Reoperation

On an actuarial basis, at 10 years, 64% ± 6% in the Carpentier-Edwards group and 59% ± 7.3% in the Hancock group have undergone reoperation (Fig 5). The difference was not significant. The linearized rates of reoperation are shown in Table 4. The causes of reoperation are listed in Table 6. The mortality for reoperation was 10% in the Carpentier-Edwards group (3/29) and 17% in the Hancock group (4/23).

Valve Failure

At 10 years, 60% ± 6.5% of the patients in the Carpentier-Edwards group and 59% ± 7.3% of those in the Hancock group were free from valve failure (Fig 6). The difference was not significant.

Causes of valve failure are listed in Table 7. It is noteworthy that in the Carpentier-Edwards group, 29 of the 34 patients with valve failure were able to have a reoperation and all the patients with valve failure in the Hancock group underwent reoperation. Seven patients in the Carpentier-Edwards group died as a result of valve failure (3, reoperation; 4, anticoagulant-related complication) and 4 in the Hancock group (4, reoperation).

Anticoagulant-Related Hemorrhage

At 10 years, 92% ± 2.7% of the patients in the Carpentier-Edwards group and 85% ± 5.5% of those in the Hancock

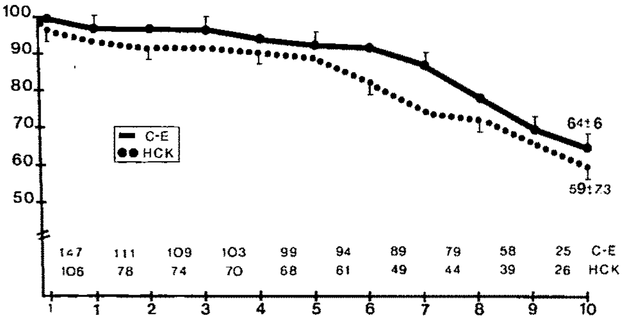

Fig 5. Actuarial curves of freedom from reoperation. (C-E = Carpentier-Edwards; HCK = Hancock.)

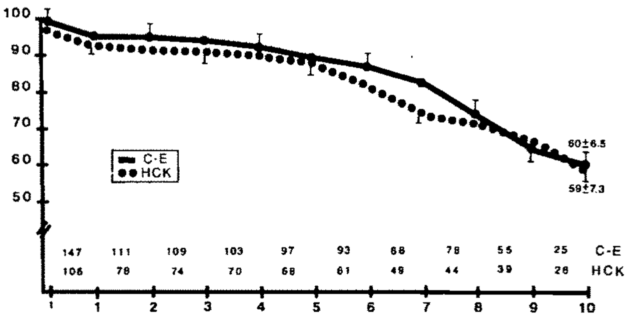

Fig 6. Actuarial curves of freedom from valve failure. (C-E = Carpentier-Edwards; HCK = Hancock.)

Table 7. Causes of Valve Failure

Cause	Carpentier-Edwards (n = 147)	Hancock (n = 106)
Structural valve deterioration	24	14
Thromboembolic complications	3	1
Periprosthetic leak	3	3
Endocarditis	0	4
Anticoagulant-related hemorrhage	4	0
Inadequate size	0	1
Total	34	23

group were free from anticoagulant-related hemorrhage (Fig 7). The difference was not significant. Linearized rates are shown in Table 4. In the Carpentier-Edwards group, 4 patients died as a result of an anticoagulant-related complication; none in the Hancock group died of this complication.

Valve-Related Mortality and Morbidity

Combining the incidence of thromboembolic and anticoagulation complications not resulting in reoperation or death with the incidence of valve failure yielded a composite function describing the incidence of valve-related mortality and morbidity. On an actuarial basis, 50% ± 7.2% of the patients in the Carpentier-Edwards group and 49% ± 7.5% of those in the Hancock group were free from valve-related complications at 10 years. This difference was not significant (Fig 8). The linearized rates are shown in Table 4.

Comment

In spite of the extensive use since 1974 of porcine bioprostheses, mainly the Carpentier-Edwards and the Hancock, few reports are available that compare the long-term results between these two valves [7–9]. Using the methods described in a previous report from our institution [10], this study seems appropriate because it compares two series of patients operated on in the same institution by the same team over a limited period of 5 years with a follow-up of 7 to 12 years. The homogeneity of the two groups has been demonstrated only on the basis of clinical findings (age, preoperative functional class, preoperative cardiothoracic ratio, predominant functional lesion, etiology), as hemodynamic data were not available on all patients.

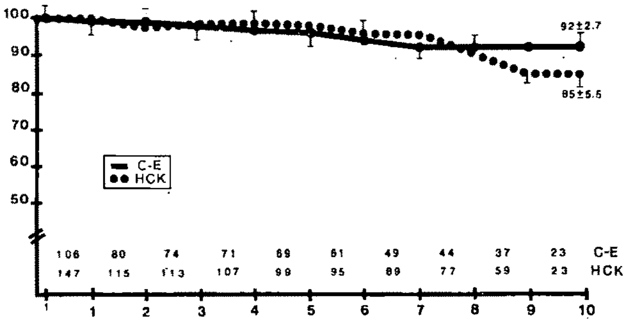

Fig 7. Actuarial curves of freedom from anticoagulant-related hemorrhage. (C-E = *Carpentier-Edwards;* HCK = *Hancock.)*

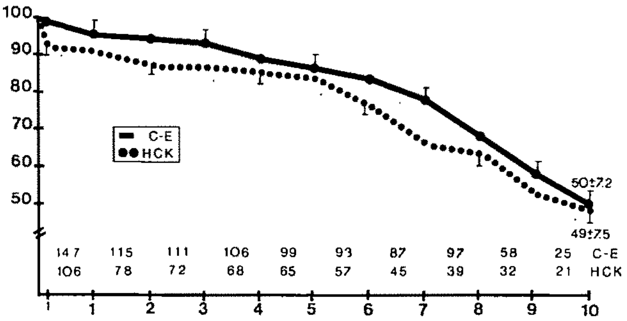

Fig 8. Actuarial curves showing percentage of patients free from valve-related mortality and morbidity. (C-E = *Carpentier-Edwards;* HCK = *Hancock.)*

One criticism that could be leveled is that the selection of the type of bioprosthesis placed was not randomized. Rather it was left to the discretion of each individual surgeon who habitually used the same prosthesis during the study period.

The operative mortality was high. However, the operative risk has improved in the past 10 years because of better myocardial protection. The current risk for isolated mitral valve replacement is 3%.

Our 10-year survival of 55% and 50% for the Carpentier-Edwards and the Hancock groups, respectively, is similar to that in other reports on bioprostheses in the mitral position [11, 12]. However, the overall late survival, which is determined by patient-related factors and mostly by the condition of the heart at the time of operation, is not a sensitive indicator of the performance of a given prosthesis.

The incidence of valve-related death may be a more accurate indicator of the risks associated with a given device. The actuarial rates of freedom from valve-related death (93% in the Carpentier-Edwards group and 85% in the Hancock group) revealed no significant difference. However, in a nonrandomized retrospective study, assessing the cause of death in a population who lived outside the hospital and who often died unobserved leads to a sustained possibility of error, as underlined by Hammond and colleagues [13]. As a result, we separated the patients who died suddenly. Most certainly, many of these patients died of an arrhythmia, but it is likely that some patients died of a valve-related cause. The computation of valve-related mortality incorporating sudden death did not yield different results.

One of the prime reasons for using porcine bioprosthetic valves is to decrease the incidence of thromboembolic complications compared with mechanical valves. As in other reports [14, 15], the rate of thromboembolic complications was low in the two groups (0.8% ± 0.3% per patient-year in the Carpentier-Edwards group and

1.1% ± 0.4% per patient-year in the Hancock group). As other studies [15, 16] have shown, most of the thromboembolic complications occurred within the first postoperative year.

The incidence of anticoagulant-related hemorrhage, 1% ± 0.3% per patient-year in the Carpentier-Edwards group and 1.3% ± 0.4% per patient-year in the Hancock group, was relatively high in this report, especially considering that 4 patients in the Carpentier-Edwards group died as a result of anticoagulation complications.

Durability remains the major problem of tissue valves, and represents a serious concern for the patient and the surgeon. At the end of 10 years, 35% of the patients in both groups have undergone reoperation for structural valve deterioration, an incidence frequently reported in the literature [11, 17–19]. As in most other reports [7, 9], no difference was observed in the rate of structural valve deterioration between the Carpentier-Edwards prosthesis and the Hancock prosthesis. One exception was the study of Hartz and co-workers [20], which suggested that the deterioration rate of the Carpentier-Edwards bioprosthesis was less than that of the Hancock valve, but the follow-up was shorter. In both groups, the first cases of structural valve deterioration began occurring in the third postoperative year.

One of the major issues with bioprostheses is the operative mortality associated with reoperation for structural valve deterioration. The operative mortality for valve re-replacement was 4% in the Carpentier-Edwards group and 21% in the Hancock group. In a larger series of 90 reoperations for structural valve deterioration of bioprostheses, we [21] found an operative mortality of 5.5%, a risk similar to that of primary operations.

It is of note that in 25% of the reoperations for structural valve deterioration, a second kind of bioprosthesis was used (usually at the request of the patient) to avoid anticoagulation, provided failure did not occur within the first 8 years after implantation. This percentage is low compared with that of Magilligan and colleagues [17], who replaced 77% of degenerated valves in the mitral position with a different bioprosthesis.

In summary, our study shows that the first-generation Carpentier-Edwards porcine bioprosthesis and the Hancock prosthesis produce comparable long-term results in the mitral position. The problem of structural valve failure in tissue valves may be eased in the recent products by the introduction of new methods of tissue preservation, low-pressure fixation, and improvements in calcium mitigation.

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Thrombotic Obstruction of Disc Valves: Clinical Recognition and Surgical Management

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Twenty-seven patients underwent reoperation because of thrombotic obstruction of a disc-type cardiac valve prosthesis. Preoperative clinical features included effort dyspnea in 81%, new-onset angina in 44%, a new murmur in 89%, and an abnormal opening or closing sound associated with the prosthetic valve in 56%. Symptoms were present for 1 week or more before reoperation in 86%, although many patients were referred only after acute exacerbation of heart failure and development of pulmonary edema. Noninvasive studies confirmed prosthetic valve malfunction in only 33%, but cardiac catheterization documented thrombotic obstruction in all 15 patients in whom it was performed. In 14 of the 27 patients, prothrombin time was in the therapeutic range at the time of admission. Prompt reoperation for valve replacement or thrombectomy was performed with an operative mortality of 11%, and long-term outcome was satisfactory in all but 1 hospital survivor. These findings emphasize the importance of considering the diagnosis of thrombosed heart valves in patients with mechanical heart valves who are seen with nonspecific symptoms.

(Ann Thorac Surg 1989;48:60–5)

Thrombotic obstruction, a rare but very serious complication of cardiac valve prostheses, appears to occur more frequently in disc valves than in other designs [1–15]. Karp and colleagues [12] reported the cumulative (actuarial estimate) risks for thrombosis of Björk-Shiley tilting-disc valves to be 3%, 13%, and 13% at 5 years after aortic, mitral, and combined aortic and mitral valve replacement, respectively; overall incidence was 8.6%. Reports have emphasized the sudden, precipitous deterioration in hemodynamics and the high mortality of reoperation in these critically ill patients [16]. Noninvasive procedures including cineradiography and echocardiography have been recommended in the diagnostic evaluation of prosthetic valve thrombosis [9, 16, 17].

Within the last 5 years, we have treated 8 patients who had thrombotic obstruction (1 has been described in detail [18]) and noted that various prodromes were apparent before hemodynamic deterioration; diagnosis during this interval should permit better results after reoperation. In this report, we describe the entire series of reoperations for thrombotic obstruction of prosthetic disc valves at this institution.

Material and Methods

We reviewed the clinical records of all patients who have undergone repair or replacement of malfunctioning disc valves at the Mayo Clinic. We selected for analysis those patients who had thrombus formation with or without fibrous tissue overgrowth on prosthetic disc valves and whose malfunctioning valve was the reason for reoperation. Reoperations were performed from May 13, 1969, through April 1, 1988. During analysis of the records, attention was focused on the severity and duration of preoperative symptoms.

Results

Clinical data on the 27 patients are summarized in Table 1. Twenty patients had had initial valve replacement at the Mayo Clinic. Thrombotic obstruction of the prosthetic valve occurred in the mitral position in 11 patients, in the aortic position in 11 patients, and in the tricuspid position in 5 patients. Fourteen patients had Björk-Shiley tilting-disc valves (nine aortic, three mitral, two tricuspid); 5 had Kay-Shiley disc valves (all mitral); 4 had the Starr-Edwards disc valve (one mitral, three tricuspid); 2 had Lillehei-Kaster prosthetic valves (one aortic, one mitral); 1 had a St. Jude valve (aortic); and 1 had an Omniscience valve (mitral).

The interval between implantation and dysfunction of the disc valve ranged from 4 to 144 months (median time, 54 months). Systemic anticoagulation with warfarin sodium was judged to be adequate (prothrombin time ≥2 times control) in 14 of the 27 patients at the time of diagnosis of disc valve thrombosis. In the remaining 13 patients, warfarin had been discontinued or used only intermittently; in these patients, the prothrombin time was nearly normal when the symptoms of congestive heart failure developed. Two of the 14 patients with therapeutically adequate systemic anticoagulation and 3 of the 13 patients with inadequate anticoagulation were also taking antiplatelet agents.

Prominent preoperative symptoms were dyspnea in 22 patients (81%) and angina in 12 patients (44%) (Table 2). Eight patients had progressive fatigability without pulmonary symptoms, and 7 patients had recent transient neurological deficits or frank stroke. Two patients denied

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Table 1. Summary of Clinical Data on Patients Undergoing Reoperation for Thrombosed Prosthetic Disc Valve

Patient No.	Age (yr)	Sex	Valve Site	Valve Type	Anti-coagulation	Interval From Insertion to Thrombosis (mo)	Other Prosthetic Valves	Reoperation	Outcome
1	68	F	Tricuspid	S-E	Adequate	93	Yes	Replacement, 23-mm porcine heterograft	Alive
2	37	F	Tricuspid	S-E	Adequate	54	Yes	Replacement, 31-mm H	Alive
3	41	F	Tricuspid	S-E	Adequate	64	Yes	Replacement, 33-mm H	Dead
4	50	F	Mitral	S-E	Adequate	36	No	Replacement, 3M S-E ball	Alive
5	37	F	Mitral	L-K	Adequate	36	No	Replacement, 3M S-E ball	Alive
6	66	M	Aortic	L-K	Inadequate	28	No	Replacement, 10A S-E ball	Alive
7	30	F	Mitral	K-S	Adequate	30	No	Replacement, 3M S-E ball	Alive
8	58	F	Mitral	K-S	Inadequate	140	No	Replacement, 31-mm B-S	Alive
9	56	F	Mitral	K-S	Adequate	96	No	Replacement, 3M S-E ball	Alive
10	47	F	Mitral	K-S	Adequate	16	No	Replacement, 6M S-C ball; replacement tricuspid valve, 3M S-E ball	Alive
11	50	M	Mitral	K-S	Adequate	128	No	Replacement, 27-mm H	Alive
12	18	F	Tricuspid	B-S	Inadequate	21	No	Replacement, 31-mm H	Alive
13	38	F	Tricuspid	B-S	Adequate	83	Yes	Replacement, 29-mm I-S	Alive
14	47	F	Mitral	B-S	Inadequate	29	No	Replacement, 27-mm C-E	Dead
15	58	F	Mitral	B-S	Adequate	144	Yes	Replacement, 3M S-E ball	Alive
16	58	M	Mitral	B-S	Adequate	108	No	Replacement, 4M S-E ball	Alive
17	66	M	Aortic	B-S	Adequate	67	No	Thrombectomy	Alive
18	57	M	Aortic	B-S	Inadequate	84	No	Replacement, 31-mm C-E; coronary artery bypass × 2	Alive
19	45	M	Aortic	B-S	Inadequate	16	No	Replacement, 25-mm C-E	Alive
20	33	F	Aortic	B-S	Inadequate	14	No	Thrombectomy	Alive
21	33	F	Aortic	B-S	Inadequate	28	Yes	Thrombectomy	Alive
22	59	M	Aortic	B-S	Inadequate	91	No	Replacement, 23-mm C-E; pericardial patch enlargement, aortic valve	Alive

(*Continued*)

Table 1. Continued

Patient No.	Age (yr)	Sex	Valve Site	Valve Type	Anti-coagulation	Interval From Insertion to Thrombosis (mo)	Other Prosthetic Valves	Reoperation	Outcome
23	54	F	Aortic	B-S	Inadequate	97	Yes	Thrombectomy; septal myotomy	Alive
24	84	F	Aortic	B-S	Inadequate	46	No	Thrombectomy	Alive
25	68	M	Aortic	B-S	Inadequate	20	No	Thrombectomy	Alive
26	26	F	Aortic	SJ	Inadequate	71	No	Thrombectomy	Dead
27	67	F	Mitral	O	Adequate	4	Yes	Replacement, 4M S-E ball	Alive

B-S = Björk-Shiley; C-E = Carpentier-Edwards; H = Hancock; I-S = Ionescu-Shiley; K-S = Kay-Shiley; L-K = Lillehei-Kaster; O = Omniscience; S-C = Smeloff-Cutter; S-E = Starr-Edwards; SJ = St. Jude.

having any symptoms at the time of presentation, and disc malfunction was suspected from the results of the clinical examination.

The duration of progression of cardiac symptoms prior to reoperation varied widely: less than 1 week, 2 patients (7%); 1 week to 1 month, 8 patients (30%); 1 to 6 months, 11 patients (41%); and more than 6 months, 4 patients (15%). The 2 patients (7%) who were seen with hemolysis were asymptomatic. In general, the symptomatic patients had severe disability. New York Heart Association classifications at the time of operation were class IV for 9 patients, class III for 10 patients, and class II for 8 patients. Four patients were in cardiogenic shock at the time of valve reoperation. However, these 4 patients, as well as the other symptomatic patients, had had milder symptoms for periods ranging from ten days to 1 year preoperatively. In several patients, the minor symptoms were initially discounted as a flulike illness, chronic obstructive lung disease, or mild congestive heart failure due to progressive left ventricular dysfunction.

The diagnosis of prosthetic valve malfunction was suspected from clinical examination and various laboratory evaluations (see Table 2). A new murmur developed in 24 patients (89%), and 15 patients had abnormal (muffled) opening or closing sounds of the prosthetic valve. Other physical findings were a neurological deficit (permanent or transient) in 5 patients and hypotension in 6 patients, 4 of whom were in overt cardiogenic shock. Two patients denied serious cardiac limitation but were noted to have severe hemolysis at the time of routine follow-up, and results of the physical examinations suggested prosthetic valve malfunction.

Diagnostic studies included chest roentgenography, the results of which were abnormal in 24 (89%) of the 27 patients (Table 3). Abnormal findings were pulmonary venous congestion in 20 patients and cardiomegaly with or without evidence of pulmonary venous hypertension in 4 patients. Fluoroscopy with cineradiography was

Table 2. Preoperative Clinical Features of Patients Undergoing Reoperation for Disc Valve Thrombosis[a]

Variable	No. of Patients
Symptoms[b]	
Dyspnea	22 (81)
Angina	12 (44)
Fatigability	8 (30)
History of TIA or stroke	7 (26)
New murmur	24 (89)
Abnormal opening or closing sound of prosthetic valve[c]	15 (56)
Hypotension[d]	6 (22)
Stroke	5 (19)
Hemolysis	2 (7)

[a] Numbers in parentheses are percentages. [b] Two patients were asymptomatic and were seen with hemolysis (patients 4 and 9; see Table 1). [c] It was a muffled sound. [d] Four were in overt cardiogenic shock.

TIA = transient ischemic attack.

Table 3. Diagnostic Studies in Patients Undergoing Reoperation for Thrombosis of Disc Valves

		Results					
		Normal		Abnormal		Indeterminate	
Study	No. of Patients	No.	%	No.	%	No.	%
Chest roentgenography	27	3	11	24[a]	89	0	0
Fluoroscopy of valve	11	7	64	4[b]	36	0	0
Echocardiography	18	3	17	6	33	9	50
Cardiac catheterization	15	0	0	15[c]	100	0	0

[a] Twenty patients had pulmonary venous congestion or pulmonary edema; 4 patients had cardiomegaly without changes in pulmonary venous pattern. [b] Poor seating and decreased excursion of valve discs were noted. [c] Positive findings included thrombus formation on valve, valvular incompetence, decreased disc mobility, and abnormal pressure gradient across prosthetic valve.

Table 4. Interval From Hospital Admission to Reoperation for Disc Valve Thrombosis[a]

Interval	No. of Patients[b]
<24 h	4 (18)
1 day–1 wk	12 (55)
1 wk–1 mo	5 (23)
>1 mo	1[c] (5)
Total	22

[a] Numbers in parentheses are percentages. [b] Five additional patients had elective surgical admission and operation (patients 4, 9, 11, 13, 18; see Table 1). [c] Operation was deferred to allow full-term delivery of pregnancy while the patient was under observation in the hospital (patient 26; see Table 1).

performed in 11 patients; in only 4 patients was decreased excursion or poor seating of the disc thought to be diagnostic of prosthetic valve malfunction. Two-dimensional echocardiograms were obtained in 18 patients; 3 patients (17%) were thought to have normal valve excursion, 6 (33%) were thought to have decreased amplitude of disc excursion with diminished opening and closing rates, and for 9 (50%) the results were considered nondiagnostic.

Fifteen patients underwent cardiac catheterization, and findings indicating prosthetic valve malfunction were seen in all. These findings included visualization of thrombus on the valve, documentation of valvular incompetence, delineation of poor disc mobility, and an abnormally high transvalvular pressure gradient.

Thus, the diagnosis of prosthetic valve thrombosis was made by cardiac catheterization in 15 patients, by echocardiography in 6 patients, and by cinefluoroscopy in 4 patients. In the remaining 2 patients, valve exploration was undertaken because of strong clinical suspicion of valve malfunction in addition to findings on noninvasive studies that were suggestive but not diagnostic of valve thrombosis.

The timing of reoperation depended on the clinical condition of the patient and the time necessary for establishing the diagnosis of thrombotic obstruction of the prosthetic valve. The delay from hospital admission to operation was less than seven days for 16 patients, and the more seriously ill patients underwent operation within 24 hours after the diagnosis was established (Table 4). A period greater than 1 week was necessary to make the diagnosis and proceed with operation in 5 patients. At reoperation, the obstructed valve was replaced in 20 patients: a bioprosthesis was used in 10 and another mechanical valve, in 10 (Starr-Edwards ball-and-cage valve, 8 patients; Björk-Shiley tilting-disc valve, 1 patient; Smeloff-Cutter ball-and-cage valve, 1 patient). Seven patients had simple thrombectomy without valve replacement. Concomitant coronary artery bypass with saphenous vein grafts was performed in 1 patient.

There were 3 deaths within 30 days after operation. One patient (patient 26) could not be weaned from cardiopulmonary bypass because of intractable biventricular failure. Another patient (patient 14) who had been in cardiogenic shock preoperatively died 24 hours postoperatively of progressive myocardial failure. The third patient sustained a cerebral embolism on postoperative day 9. This 41-year-old woman had previously undergone mitral valve replacement with a 3M Starr-Edwards ball valve and tricuspid valve replacement with a 3M Starr-Edwards disc valve. The thrombosed tricuspid valve was replaced with a 33-mm Hancock prosthesis, and the patient had a good hemodynamic result until the sudden embolism.

Nonfatal complications occurred in 4 patients. Three required reexploration in the early postoperative period because of excessive hemorrhage, and a permanent transvenous pacemaker was necessary in 1 of them because of postoperative complete heart block. Another patient had anoxic encephalopathy as a result of cardiac arrest immediately prior to operation. His postoperative course was complicated by aspiration pneumonia necessitating tracheostomy.

Comment

The reported incidence of Björk-Shiley valve thrombosis ranges from 1% to 8% [1–15]; thrombotic complications with other disc valves have not been defined as completely. Patients with prosthetic aortic or mitral valve thrombosis can have dyspnea for one day to 1 week prior to presentation, with precipitous deterioration of hemodynamic function, usually within hours after hospital admission [9, 16, 17]. However, more recent reports [19 20] reveal a rapid catastrophic symptomatic course associated with disc valve thrombosis with only an occasional longer prodrome. The most salient finding on clinical examination of these patients is the absence or attenuation of the prosthesis-related opening or closing sound. Nonspecific clinical findings include systolic and diastolic murmurs and hemolytic anemia. Inadequate systemic anticoagulation has been the single most important contributing factor to valve thrombosis [9, 17].

The important finding in this review was the chronicity of symptoms before presentation. Seventy percent of patients had clinical evidence of valve malfunction for 1 week to 6 months prior to reoperation, although many patients had acute deterioration just before presentation. These results are especially pertinent for physicians who are responsible for the follow-up of patients with prosthetic valves. Relatively minor symptoms, especially pulmonary congestion, should prompt a careful cardiac examination to exclude the possibility of prosthetic valve thrombosis.

Fluoroscopy (with cineradiography) and echocardiography have been used as adjunctive noninvasive diagnostic procedures for the documentation of prosthetic valve thrombosis [9, 16, 17]. Fluoroscopy in 11 of our patients with thrombosed prosthetic valves resulted in a false-negative rate of 64%. Visualization of the disc by cineradiographic and fluoroscopic techniques in two planes simultaneously has been shown to increase the accuracy of detecting disc valve malfunction [21]. Echocardiography had a 17% false-negative rate in the 18 patients evaluated; moreover, 50% of the patients had an indeterminate result on diagnostic echocardiographic study. With the combined application of echocardiography and Doppler studies in the evaluation of disc valves, thrombotic obstruction of the prosthetic valve can be more easily discerned.

Despite the small number of patients undergoing the studies, fluoroscopy and standard echocardiography appear to be less sensitive diagnostic methods in ascertaining prosthetic disc valve thrombosis. Cardiac catheterization continues to be the standard diagnostic procedure in the evaluation of a patient who is in hemodynamically stable condition and is suspected of having prosthetic valve thrombosis [9].

This study included all forms of thrombosed prosthetic disc valves confirmed at operation. The specific type of valve is probably a reflection of the time course of this retrospective analysis. Unlike previous reports [17], in our series, half of the patients were documented to have had adequate anticoagulation at the time of presentation. However, occasional discontinuation of anticoagulant therapy at some time in the patient's history may have been associated with a rebound hypercoagulable state, which has been reported to result in an increased rate of thromboembolic complications [22].

Surgical treatment of disc valve thrombosis includes both thrombectomy and replacement of the prosthetic valve [9, 20, 23–25]. In select circumstances of thrombosis of disc valves in the tricuspid position, thrombolytic therapy has been successful in restoring normal prosthetic function early [26, 27], but this approach would not be expected to affect fibrous ingrowth, which may be the underlying cause of valve thrombosis.

The reported mortality from prosthetic valve thrombosis ranges from 33% to 100% [3, 5, 7–9, 11, 12]. With most patients (73%) having valve replacement or thrombectomy soon after admission, a mortality rate of 11% was noted in this study. This is close to the 8% mortality reported by Copans and associates [16] in patients who underwent operation four to six hours after admission.

The clinical manifestations of prosthetic disc valve thrombosis are indolent, progressive, and protean; any patient with a mechanical heart valve, especially a tilting-disc prosthesis, who is seen with nonspecific cardiac symptoms should undergo a thorough evaluation to rule out the possibility of thrombotic obstruction of the prosthesis. For most patients, early reoperation will give the best late results. In patients who are in stable condition preoperatively, operative mortality is low.

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Notice From the Southern Thoracic Surgical Association

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Phoenician Golf and Tennis Resort, Scottsdale, AZ, November 9–11, 1989. There will be a $155 registration fee for the Scientific Session for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 9, 1989. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Advance registration forms, hotel reservation cards, and details regarding transportation arrangements will be mailed to Association members. Nonmembers should write to the Secretary-Treasurer, Gordon F. Murray, MD.

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Thoracoscopy: A Review of 121 Consecutive Surgical Procedures

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The records of 121 patients who underwent surgical thoracoscopy between 1976 and 1987 were reviewed. The indications for thoracoscopy were pleural effusion (88%), pleural thickening (7.4%), and a mass on the chest roentgenogram (15%). All procedures were performed under general anesthesia with a rigid thoracoscope and 91 patients (75%) were diagnosed as having a malignant process. Although thoracotomy was undertaken in 20 patients (16.5%), no patient with benign disease underwent diagnostic thoracotomy. Thoracoscopy had a 98.9% sensitivity and a 93.3% specificity in this series. One patient died of a myocardial infarction after the procedure, and 11 patients (9.1%) had other, predominantly respiratory, complications. We confirm that surgical thoracoscopy is a useful procedure in the diagnosis of pleural processes.

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Thoracoscopy is a well-defined technique of proven value in the investigation, diagnosis, and staging of intrathoracic disease. Following initial diagnostic applications, it was introduced into clinical practice as a therapeutic procedure for the division of apical pleural adhesions in collapse therapy for pulmonary tuberculosis (apical pneumonolysis) [1]. After the introduction of successful antituberculosis chemotherapy, the number of thoracoscopies performed declined.

Recently there has been a renewed interest in thoracoscopy with local anesthesia [2]. We reviewed the records of 121 consecutive patients undergoing thoracoscopy under the care of one surgeon, and consider its indications and results.

Material and Methods

Patient Population

The case records of 121 consecutive patients who underwent thoracoscopy under the care of one thoracic surgeon (R.J.D.) in the 10-year period 1976 to 1987 were examined. There were 99 men (82%) and 22 women (18%) with a mean age of 58.1 years (range, 24 to 77 years). The indications for thoracoscopy were undiagnosed pleural effusion, pleural thickening, and further investigation of a peripheral mass visible on the chest roentgenogram. Nearly all the patients had undergone prior pleural aspiration and biopsy with inconclusive results.

The presenting symptoms in the 121 patients were the following: dyspnea on exertion, 94 patients (78%); chest pain, 64 (53%); cough, 36 (30%); and hoarseness, 4 (3%). Some patients had more than one presenting symptom. Chest roentgenograms revealed a pleural effusion in 88% of the patients (107 patients), pleural thickening in 7.4% (9 patients), and a solid mass in 15% (18 patients). The majority of these last patients were seen at the beginning of the series when the technique was used as a staging procedure in bronchial carcinoma.

Operative Technique

During general anesthesia with full relaxation, a double-lumen endobronchial tube (Robertshaw) was introduced. The patient was then positioned for a formal lateral thoracotomy, prepared, and draped. The ipsilateral lung was not ventilated. The site of the effusion was confirmed using a syringe and needle, and a cytological specimen was obtained. Through a single stab incision, a trocar was introduced.

Any further pleural effusion was drained and air was introduced into the pleural cavity, thus allowing nonadherent lung to collapse. With a rigid thoracoscope (model D-7200; Karl Storz KG, Tuttlingen, West Germany), both visceral and parietal pleural surfaces were carefully inspected. If necessary, another stab incision was made and another trocar introduced. A sucker or probe could be passed through this to manipulate the lung and improve the view. Biopsy specimens were obtained of any suspicious areas.

If later thoracotomy was thought not to be indicated, chemical pleurodesis with either tetracycline (1 g in 50 mL of saline solution) or a cytotoxic agent (bleomycin sulfate in 3 patients and cyclophosphamide in 1 patient) was performed. After the trocar was removed, a single 28F intercostal drain was introduced through the initial stab incision, and the lung was reinflated.

Results

Examinations were performed on the right side in 63 patients (52%) and on the left in 58 (48%). One hundred seven patients had pleural effusions, 50% of which were blood stained.

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The results of thoracoscopy for the malignant and nonmalignant disease groups are shown in Tables 1 and 2. In Table 1, the final diagnosis includes information available from follow-up thoracotomy and postmortem examination. A false-negative result indicates failure to diagnose malignancy at thoracoscopy, although malignant tumor was subsequently diagnosed. Conversely, a false-positive result indicates an incorrect diagnosis of malignancy when none was present. The predictive value [3] of this "thoracoscopy-aided diagnosis," which includes data gained from clinical features, radiological findings, macroscopic appearances at thoracoscopy, and histological results, was as follows: sensitivity, 98.9%; specificity, 93.3%; accuracy, 97.5%; predictive value of a positive test, 97.8%; and predictive value of a negative test, 96.5%.

Twenty patients (16.5%) had thoracotomy. In 6 patients, thoracoscopy was unsuccessful because of failure to enter the pleural cavity on account of the depth of the thickened parietal pleura. Five of these patients immediately underwent a limited thoracotomy for diagnosis. A further 15 thoracotomies were subsequently performed: three for further evaluation of tumor extension, 11 for pleurectomy or decortication, and one for lobar resection.

One patient died after the procedure. He had extensive coronary artery disease and sustained a fatal myocardial infarction seven hours after the procedure.

Morbid complications of the procedure occurred in 11 patients (9.1%). Respiratory complications developed in 4 patients (3.3%), 2 of whom required intensive care and mechanical ventilation for up to 48 hours. Both made a good recovery and were discharged home. There were four persistent air leaks, all of which sealed with conservative management between 1 and 2 weeks after thoracoscopy. None of the 4 patients had undergone a lung biopsy.

One patient (0.8%) with a vascular undifferentiated carcinoma bled from the pleural biopsy site and required transfusion with 3 units of blood. Tumor seeding at the chest wall incision occurred in 2 patients (1.7%) with mesothelioma some months after thoracoscopy. At that time, these patients also had further evidence of metastatic spread of disease.

Table 1. Results of Thoracoscopy in Malignant Conditions[a]

Final Diagnosis	Histology		Failed	Total	False-Negative Result
	Positive	Negative			
Mesothelioma	21	14	0	35	1
Adenocarcinoma	16	0	0	16	0
Undifferentiated carcinoma	25	8	1	34	0
Squamous carcinoma	0	0	2	2	0
Others	2	0	1	3	0
Total	64	22	4	90	1

[a] See Results section for details.

Table 2. Results of Thoracoscopy in Nonmalignant Conditions

Clinical Finding	Diagnosis	No. of Patients	False-Positive Results for Malignancy
Effusion	Rheumatoid	2	0
	Hemothorax	1	0
	Meigs' syndrome	1	
	Cardiac failure	1	0
	Tuberculosis	1	0
	Idiopathic	8	0
	Postpneumonic	6	2
Fibrosis	Idiopathic	7	0
Mass on chest roentgenogram	Fibroma	2	0
	Aneurysm	1	0
Total		30	2

Comment

Thoracoscopy has found many applications, both diagnostic [4–9] and therapeutic [10], since it was described by Jacobeus in 1910 [11]. In our experience, it was first used as a staging procedure for patients with bronchial carcinoma with an effusion to avoid unnecessary thoracotomy in those with inoperable pleural involvement. However, in the majority of patients, thoracoscopy has been used for the further investigation of undiagnosed pleural effusions and thickening.

Thoracoscopy usually followed unhelpful bronchoscopy and pleural aspiration and biopsy performed in other medical units in the region. Thus, our group of patients was select and is not representative of all patients seen with pleural effusion or thickening. This may explain the high rate of malignancy in our series, 75% or 91 of 121 patients.

Adenocarcinoma, whether primary or secondary, was histologically correctly diagnosed in all patients. However, other tumors were less easily diagnosed. Combining other information with thoracoscopic appearances and histology, we correctly diagnosed all the malignant tumors in the series except one. This single false-negative finding was in a patient who had minor pleural thickening on chest roentgenograms and benign appearances at thoracoscopy. Biopsy specimens obtained at that time showed nonspecific inflammation. This initial impression proved to be incorrect; 6 months later, tumor seeding developed at the incision, and the biopsy specimen demonstrated mesothelioma. Thirty-four of the 35 cases of mesothelioma were correctly diagnosed by visual impression at thoracoscopy, although the positive-histology biopsy rate was low (60%), possibly reflecting the difficulty of histological diagnosis of this condition. Forty-seven percent of patients who gave a history of asbestos exposure were eventually diagnosed as having mesothelioma.

With the nonmalignant conditions, we again found that thoracoscopy was useful in excluding malignant tumors.

There were 2 patients in this group who were initially thought to have malignancy at thoracoscopy (false-positive result). Neither patient underwent thoracotomy, and both patients were well on follow-up. In his extensive review of thoracoscopy, Bloomberg [12] noted that normal findings in the absence of malignancy constitute a positive result from the procedure, and are more important in some cases than the results of biopsy if thoracotomy can be subsequently avoided for the diagnosis of benign disease. In none of our patients was thoracotomy performed for the diagnosis of benign disease.

There were three serious complications of the procedure in our 121 patients. The patient who died and the 2 who required ventilation are evidence that thoracoscopy is not without risk in sick patients.

We did not find the other complications of air leak and tumor seeding to be major problems. All air leaks resolved with conservative management, and although visceral pleural biopsies were not carried out in any of these patients, we believe this can safely be performed if indicated. Only 2 cases of tumor seeding occurred, and because the patients were asymptomatic, we did not think that prophylactic radiotherapy to the stab incision site was indicated, as recommended by some groups [13].

Bleeding necessitating transfusion occurred in only 1 patient. He did not undergo thoracotomy because the tumor was widely disseminated over the chest wall. However, we believe the complications that do occur with thoracoscopy are best dealt with by surgeons who are familiar with the management of persistent air leak and intrathoracic hemorrhage.

Various instruments have been suggested for thoracoscopy including the sigmoidoscope, laparoscope, and mediastinoscope [5, 14, 15]. The fiberoptic bronchoscope has been advocated by some groups [2, 16] and has attractions for physicians when the procedure can be carried out under local anesthesia with comparable diagnostic accuracy. Others [6, 17] have recommended regional anesthesia. We employ general anesthesia and find it most useful when combined with the use of a double-lumen tube, which allows the lung to completely collapse and permits a more thorough inspection of the thoracic cavity. It is also possible to perform immediate thoracotomy if a complication occurs or if safe insertion of the trocar and cannula cannot be achieved and histological results cannot otherwise be obtained.

The size of the incision for thoracoscopy varies from 1 cm to admit only a trocar and cannula (as in this series) to a larger incision up to 5 cm (as in some reports) [14]. We do not find such wider exposure to be necessary.

Our success rate is comparable with that in other reported series [2], and the use of thoracoscopy in conjunction with other diagnostic aids has been shown to be of considerable value.

In conclusion, we have found surgical thoracoscopy to be an accurate, sensitive, and specific investigation useful in the diagnosis of malignant and nonmalignant intrathoracic disease without the need for diagnostic thoracotomy.

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Right Thoracotomy, Femorofemoral Bypass, and Deep Hypothermia for Re-replacement of the Mitral Valve

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Ten patients underwent mitral valve re-replacement for the third to sixth time through a right thoracotomy using one-lung anesthesia, femorofemoral bypass, profound systemic hypothermia, and low-flow perfusion without aortic cross-clamping or cardioplegia. The indications for this approach were previous mediastinitis, severe right ventricular hypertension with multiple previous sternotomies, intact coronary artery bypass graft, or previous aortic valve replacement. There was 1 operative death, which was due to end-stage pulmonary hypertension and intractable right heart failure. Blood loss was minimal, and there was no major postoperative morbidity in the 9 surviving patients except for supraventricular arrhythmias.

(Ann Thorac Surg 1989;48:69–71)

A number of patients requiring multiple (three or more) re-replacement of the mitral valve for dysfunctional prosthetic and bioprosthetic valves [1–4] have had previous mediastinal infections or other wound-healing complications, severe right ventricular hypertension, or multiple previous sternotomies for other cardiac operations such as aortic valve replacement or coronary artery bypass grafting. The risk of multiple valve re-replacement operations may be higher than primary or first-time re-replacement, especially if the patient is in functional class IV [5–7]. The morbidity is often due to the repeat sternotomy with injuries to the right ventricle [8–9], prolongation of the operation with increased blood loss, and difficult exposure because of intense adhesions and fibrosis of cardiac structures. Though all primary and the vast majority of secondary valve operations are performed through a median sternotomy in our clinic, we report here a technique that combines a thoracotomy with perfusion techniques and results in better exposure of the mitral valve and reduced morbidity after multiple mitral valve re-replacements.

Material and Methods

Patient Population

In a 24-month period, 10 patients underwent mitral valve re-replacement through one approach for the third to sixth time. Patient data are summarized in Table 1. There were 6 women and 4 men ranging in age from 25 to 66 years (mean age, 50 years). The previous number of operations ranged from 2 through 5, all performed through a sternotomy. The mean functional class was 3.8. The original etiology was rheumatic heart disease in 7, coronary artery disease in 2, and congenital heart disease in 1.

Operative Technique

A right anterolateral thoracotomy was made through the fourth intercostal space (after one-lung anesthesia was performed with a divided endotracheal tube). The pericardium was identified and an incision made superior to the phrenic nerve. The left atrium and right atrium were exposed by reflecting the pericardium (Figs 1A, B). In all patients, femorofemoral bypass was instituted through the right groin vessels with a long inferior vena cava cannula and an arterial infusion cannula. An additional right atrial cannula (into the superior vena cava) can be placed for more complete drainage of the systemic venous return. The aortic root was not dissected out in any patient, nor was the aorta cross-clamped or cardioplegia administered.

The patient was placed on cardiopulmonary bypass and cooled to 20°C. If there is any aortic regurgitation (which was present to a minimal degree in 3 patients), the flow during valve replacement can be lowered to 200 mL/min for short periods if regurgitant blood obscures the operative field. In all patients, the mitral valve was exposed with relative ease through a left atrial incision made above the right superior pulmonary vein, removed, and replaced with a St. Jude valve using interrupted pledgeted mattress sutures of 2-0 Ethibond (Figs 1C, D). The prosthetic valve was aligned perpendicular to the horizontal axis of the mitral valve. After the valve was seated, a red-rubber catheter (10F) was inserted through the open leaflets into the left ventricle to keep one leaflet insufficient (Figs 1E, F).

The patient was then positioned in a slightly head-down, leftward position so that the left atrium was the

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Table 1. Summary of Patient Data

Patient No.	Age (yr)	Sex	Original Diagnosis	Operative Diagnosis	No. of Previous Operations
1	29	F	Congenital heart disease	Degenerated bioprosthetic valve	4
2	42	F	Rheumatic heart disease	Degenerated bioprosthetic valve	2
3	25	M	Rheumatic heart disease	Degenerated bioprosthetic valve	2 (Previous mediastinitis)
4	64	F	Coronary artery disease	Degenerated bioprosthetic valve	2 (CABG, patent)
5	66	F	Rheumatic heart disease	Degenerated bioprosthetic valve	5
6	27	F	Rheumatic heart disease	Degenerated bioprosthetic valve	4
7	57	M	Coronary artery disease	Degenerated bioprosthetic valve	3 (CABG, patent)
8	64	M	Rheumatic heart disease	Paravalvular leak	2
9	64	F	Rheumatic heart disease	Degenerated bioprosthetic valve	3
10	65	M	Rheumatic heart disease	New mitral stenosis	2 (Previous AVR)

AVR = aortic valve replacement; CABG = coronary artery bypass grafting.

most superior aspect of the left heart. The left atrium was closed with running 3-0 Prolene sutures, and the heart was externally defibrillated using previously placed external defibrillator electrodes. In three instances, patients spontaneously defibrillated with rewarming.

Once the patient reached normal temperature, partial bypass was begun with the interruption of one of the caval cannulas. As the heart filled, blood and air were ejected through the red-rubber catheter from the left ventricle and the left atrial incision. Because the mitral

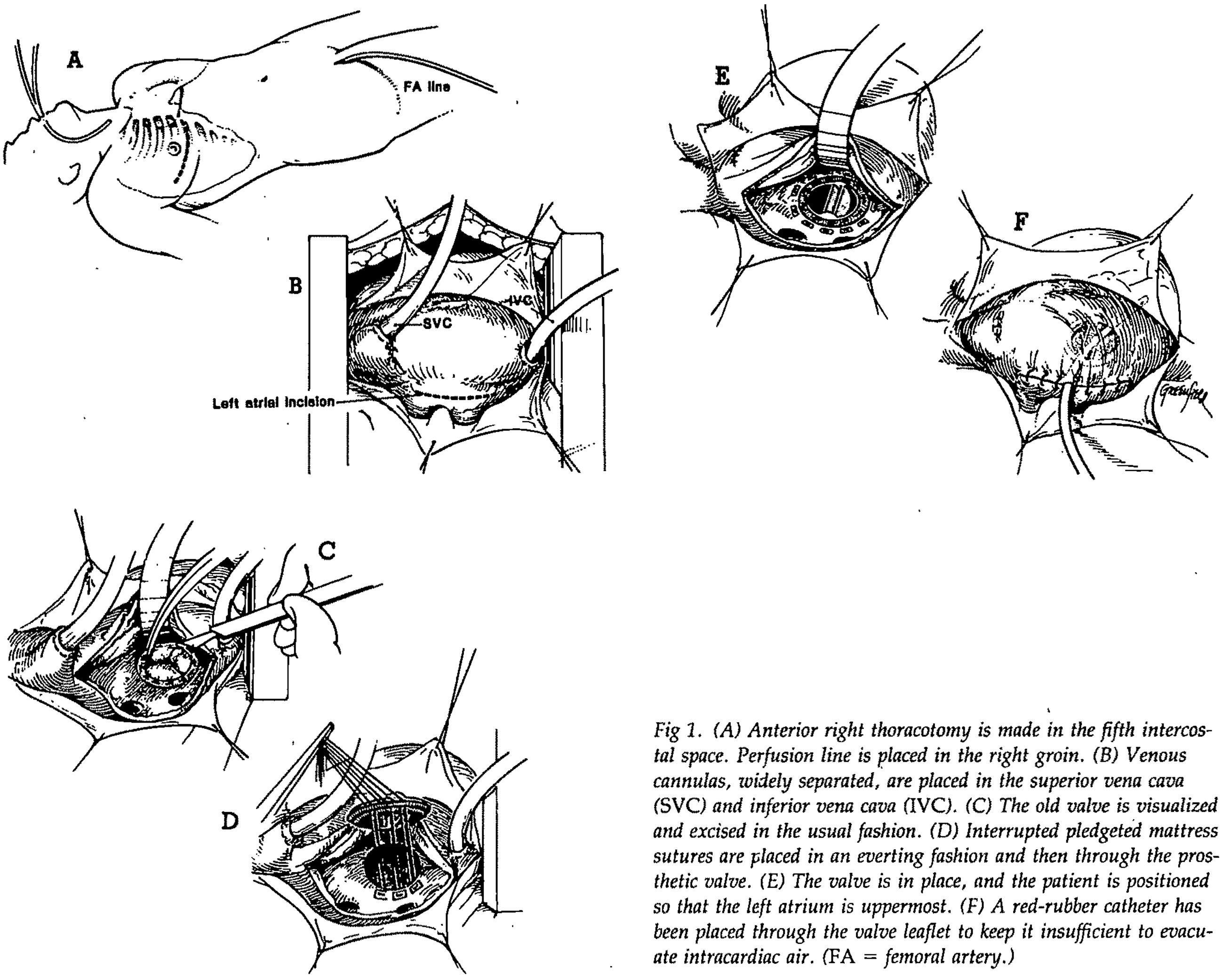

Fig 1. (A) Anterior right thoracotomy is made in the fifth intercostal space. Perfusion line is placed in the right groin. (B) Venous cannulas, widely separated, are placed in the superior vena cava (SVC) and inferior vena cava (IVC). (C) The old valve is visualized and excised in the usual fashion. (D) Interrupted pledgeted mattress sutures are placed in an everting fashion and then through the prosthetic valve. (E) The valve is in place, and the patient is positioned so that the left atrium is uppermost. (F) A red-rubber catheter has been placed through the valve leaflet to keep it insufficient to evacuate intracardiac air. (FA = femoral artery.)

valve could not close, there was no substantial forward flow until the catheter was removed. Finally, the patient was weaned from bypass with both lungs inflated and ventilated. After all air was removed, the final stitch in the left atrial suture line was closed and the patient was weaned totally from cardiopulmonary bypass. Bypass times ranged from 75 to 100 minutes (mean time, 90 minutes). Left and right atrial lines and right ventricular pacing wires were placed, chest tubes were placed in the right chest, and the chest was closed in the usual fashion.

Results

Nine of the 10 patients survived the operation. One patient died of severe pulmonary hypertension from end-stage pulmonary artery disease and right heart failure intraoperatively. In no patient was there any sign of central nervous system dysfunction, a finding that would suggest incomplete evacuation of air. Postoperatively 4 patients had supraventricular tachycardias, which were treated medically. The 9 survivors are well 2 to 22 months postoperatively. The 2 with bypass grafts from previous operations had no evidence of myocardial ischemia.

Comment

A thoracotomy was used in the 1940s, 1950s, and 1960s for both closed and open mitral valve operations [10, 11]. Median sternotomy became the incision of choice for open-heart surgical procedures in the late 1960s because it was recognized that intracardiac air was more completely removed. Also, any anatomical variant was clearly demonstrated to be better handled by this incision than from either side, and myocardial protection was much better implemented through the ascending aorta.

Patients undergoing the third to sixth valve rereplacement, however, require some special considerations. They have very severe adhesions around the heart, thus making bleeding a serious problem and making anatomical access to the very scarred and densely adherent left atrium difficult. The right thoracotomy approach is associated with minimal blood loss postoperatively and affords better exposure to the left atrium in these high-risk patients with a difficult anatomy.

The fact that the aorta is not exposed and there is no aortic vent and no cardioplegia is controversial. Many have used ventricular fibrillation and no cardioplegia for many years in all types of operations, but overall, cardioplegia has clearly been enormously beneficial. Cardioplegia does afford better overall myocardial protection, but in this particular situation, profound hypothermia with low-flow blood perfusion is a quite satisfactory alternative, as most of these patients had no concomitant coronary artery disease. If they did, it had been completely corrected. With low perfusion flow and profound systemic hypothermia, myocardial protection has been excellent in this particular subset of patients. Low-flow cold blood perfusion of coronary arteries produces complete standstill of the heart at these temperatures. If other operative procedures such as coronary bypass grafting or aortic valve replacement need to be done, this approach is not feasible. Tricuspid valve replacement, however, is quite possible through this approach and was accomplished in 1 patient (patient 5).

Prevention of air embolism is a major concern, but with the positioning of the patient and by making the new mitral valve incompetent, residual air in the left ventricle should rise through the vent and the left atrial incision. Because there is no interruption of aortic flow, there is no air collecting in the ascending aorta unless flow is completely interrupted, which is not done. If the aortic valve is slightly insufficient, this helps fill the ventricle and express air from the most superior portion of the incision, in this case, the anterolateral aspect of the left atrium.

This approach has been described for reoperations on the mitral valve in patients who have had prior mitral valve replacement plus repair of other lesions. In a series reported by Berreklouw and Alfieri [12], aortic clamping and cardioplegia were used, and all patients survived without major postoperative morbidity except right pleural effusions.

In select situations in patients with mitral valve disease, the operative approach presented here has been helpful. For patients with isolated mitral valve disease who require mitral valve re-replacement for the third time (or more) or for patients with patent bypass grafts or sternotomy complications, this approach should be considered.

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Serial Changes in Renal Function in Cardiac Surgical Patients

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Cardiopulmonary bypass is widely believed to be injurious to renal function. The low incidence of renal dysfunction with modern techniques of bypass led us to reexamine this concept by monitoring urine output and creatinine clearance in 18 adult patients undergoing nonpulsatile, hemodilution cardiopulmonary bypass for coronary artery bypass grafting (12 patients) or valve procedures (6 patients). Samples were taken before, during (mean duration of bypass, 105 ± 26 minutes [± standard deviation]), and every two hours after bypass for 24 hours. Urine output (42 ± 37.7 mL/h) and creatinine clearance (57 ± 40.4 mL/min) were surprisingly low in the period before cardiopulmonary bypass (all values normalized to a body surface area of 1.73 m^2). Urine volumes rose to 305 ± 149.6 mL/h and creatinine clearance to 252 ± 176.9 mL/min during bypass and decreased to stable values after eight hours in the postoperative unit (urine output, ≈60 mL/h, and creatinine clearance, ≈75 mL/min). Renal dysfunction did not develop in any patient. Nine patients who required loop diuretics for low urine output 18 hours postoperatively had a sustained increase in both urine output and creatinine clearance lasting up to six hours. We conclude the following: modern techniques of cardiopulmonary bypass are not injurious to renal function; urine output and creatinine clearance are decreased before cardiopulmonary bypass, probably because of preoperative dehydration; and loop diuretics in the postoperative period increase both urine output and creatinine clearance for as long as six hours after administration.

(Ann Thorac Surg 1989;48:72–6)

Cardiopulmonary bypass has long been thought to have deleterious effects on renal function [1]. This impression was supported by both clinical and experimental studies in the first two decades of open heart surgery [2–7]. Many of the patients had congestive heart failure and persistent low cardiac output. Techniques of anesthesia and cardiopulmonary bypass were different, including blood primes, longer pump runs, and methods of fluid and drug management. This early experience, however, may no longer be applicable to today's patients; postoperative renal failure and renal dysfunction are now uncommon. The present clinical study was undertaken to examine serial changes in renal function before, during, and after cardiopulmonary bypass.

Material and Methods

The study group consisted of 18 adult patients, 10 men and 8 women, with a mean age of 64.9 ± 11.5 years (± standard deviation) (range, 28 to 80 years). Twelve patients were scheduled to undergo coronary artery bypass grafting; 3, mitral valve replacement or commissurotomy; and 3, aortic valve replacement. The first patient in the morning in one operating room was chosen for convenience and to standardize the time that the patient had been without oral intake. The study protocol was approved by the Human Subjects Review Committee on November 16, 1987, and informed consent was obtained from all patients.

There were 14 study intervals: before cardiopulmonary bypass, ie, from the time of insertion of the Foley catheter until the start of cardiopulmonary bypass; bypass, ie, the entire period of cardiopulmonary bypass; and every two hours after the arrival of the patient in the postoperative unit for 24 hours.

Sample Collection

Blood specimens were collected in the operating room before induction of anesthesia, 15 minutes after the start of cardiopulmonary bypass, and every two hours after arrival in the postoperative unit for 24 hours. Urine specimens were collected after insertion of the Foley catheter; the contents of the bladder at the time of insertion were discarded. The first collection period was from insertion of the urinary catheter until the start of cardiopulmonary bypass. The second included the entire period of cardiopulmonary bypass. Subsequent urine collections were made every two hours after arrival in the postoperative unit. Ten-milliliter aliquots of urine were collected in tubes containing 100 mg of boric acid (as a preservative) and stored in a refrigerator until analysis. Urine volume was measured by an electronic collection system (C.R. Bard, Inc, Covington, GA), which automatically records urine volume and time.

Laboratory Methods

Urine and serum creatinine values were determined with a commercial reagent kit (Sterling Biochemical, Inc, Troy,

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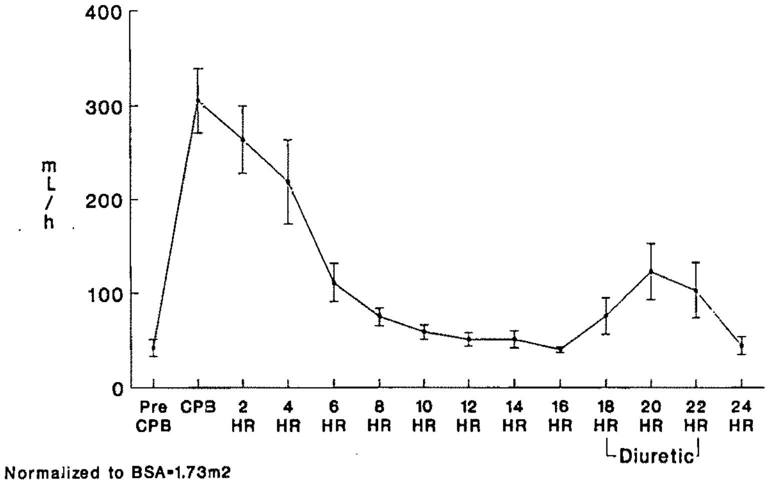

Fig 1. Urine output in all patients. Starting at 18 hours, 9 of the 18 patients were given diuretics for urine output of less than 40 mL/h. (BSA = *body surface area;* Pre CPB = *time from insertion of Foley catheter to start of cardiopulmonary bypass;* CPB = *entire period of cardiopulmonary bypass;* 2 HR, *etc* = *two hours after arrival in postoperative unit, etc; error bars* = ± *one standard error.)*

MI), which uses a modification of the method of Heinegard and Tiderstrom [8]. Blood was allowed to clot and centrifuged at 2,000 rpm for 15 minutes; the serum was separated immediately. Analyses were performed on fresh sera after collection (or the sera were stored at −70°C for up to a week) because of the lability of creatinine. The between-run precision of this method is ±5% for creatinine values between 0 and 15 mL/dL (n = 20).

Creatinine Clearance

Creatinine clearance was determined by the standard formula: creatinine clearance (mL/min) = (urine creatinine concentration [mg/mL] × urine volume [mL/min])/plasma creatinine concentration (mg/mL). The serum creatinine level at the start of each period was used to determine the creatinine clearance during that period. This value was used, rather than the average of the creatinine values surrounding each period, to avoid a possible error that might be introduced by hemodilution if the sample taken during cardiopulmonary bypass were averaged with the specimen obtained before cardiopulmonary bypass. It was found that using the average of the creatinine levels at the beginning and end of each period had no appreciable effect on the calculated creatinine clearances. All creatinine clearances and urine outputs were normalized for a standard body surface area of 1.73 m^2. The preoperative creatinine value averaged 1.2 ± 0.33 mg/dL (range, 0.6 to 2.1 mg/dL).

Cardiopulmonary Bypass

Cardiopulmonary bypass equipment consisted of a Cobe/Stöckert roller pump (Cobe, Lakewood, CO), a Bentley (American Bentley, Irvine, CA) or Sarns (Sarns, Ann Arbor, MI) hollow-fiber membrane oxygenator, and Bentley prebypass and Pall (Pall, East Hills, NY) arterial line filters. A crystalloid prime was used, consisting of 1,000 mL of 6% hetastarch in 0.9% saline solution, 700 to 1,200 mL of Plasmalyte-A (Travenol, Deerfield, IL), 12.5 g of mannitol, 1 g of methylprednisolone, and 4,000 U of heparin, to obtain hemodilution to a hematocrit of approximately 26%. Flow was maintained at 2.2 to 2.8 L/min/m^2 at a temperature of 28°C during the period of cross-clamping; the patient was warmed to 37°C thereafter. The mean time of cardiopulmonary bypass was 104.9 ± 26.1 minutes (range, 59 to 157 minutes).

Anesthesia Technique

Standard techniques were used. Fentanyl (70 to 75 μg/kg) or sufentanil citrate (7 to 8.5 μg/kg) were given intravenously for anesthesia, vecuronium bromide was adminis-

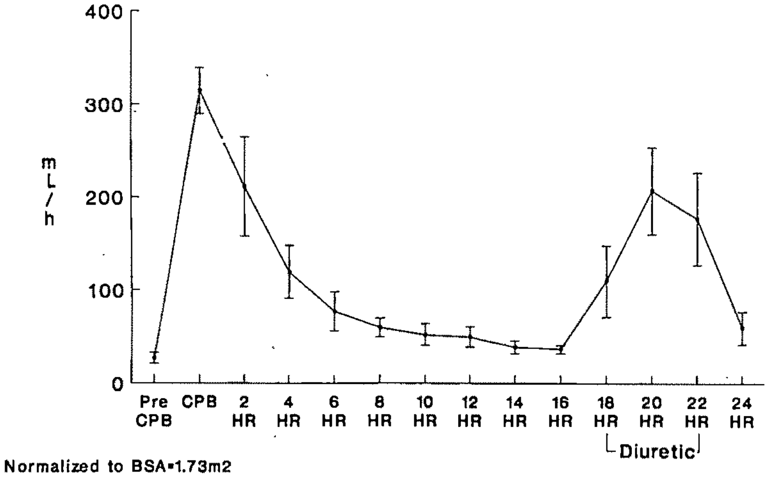

Fig 2. Urine output for the 9 patients who required diuretics in the postoperative period. (Abbreviations are the same as in Figure 1.)

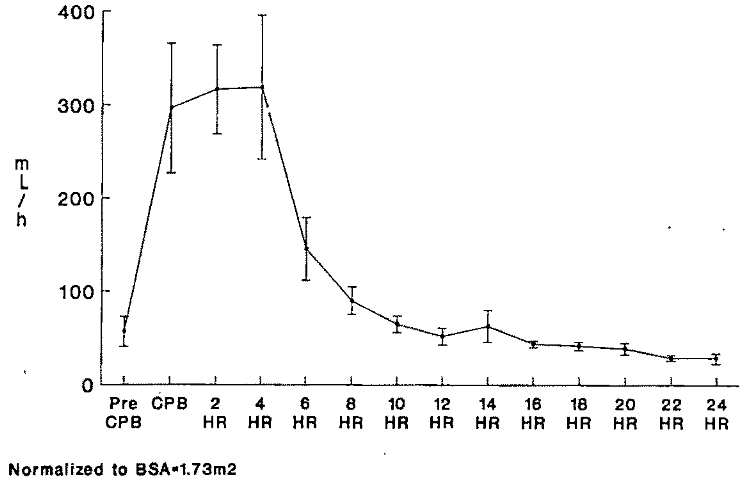

Fig 3. Urine output for the 9 patients who did not require diuretics postoperatively. Note the small standard errors starting at 8 hours. (Abbreviations are the same as in Figure 1.)

tered intravenously for muscle relaxation, and midazolam hydrochloride, for amnesia.

Diuretics

If urine output dropped to less than 40 mL/h in the postoperative period, furosemide (8 patients) or bumetanide (1 patient) was administered intravenously. No patients were given these diuretics intraoperatively.

Results

Urine output (normalized to a body surface area of 1.73 m^2) is illustrated in Figure 1. The urine output before cardiopulmonary bypass was surprisingly low, with a median of 38 mL/h and with one third of the patients having an output of less than 18 mL/h. Urine output during cardiopulmonary bypass was extremely high, averaging 306 mL/h. This diuresis was maintained well into the postoperative period, averaging 264 mL/h at two hours and 220 mL/h at four hours in the postoperative unit. Thereafter, urine outputs decreased to 50 to 60 mL/h until 18 to 22 hours, when 9 of the 18 patients required diuretics for urine output less than 40 mL/h (actual value, not corrected for body surface area). The effect of diuretics at these times can be seen in Figures 2 and 3 in which urine outputs of patients who did not require diuretics and those who did are displayed separately. The effect of the diuretics lasted for four to six hours.

The creatinine clearances closely paralleled the urine outputs and are shown in Figures 4 through 6. Prior to bypass, the mean creatinine clearance was 57 ± 40.4 mL/min (± standard deviation) (normalized to a body surface area of 1.73 m^2); it increased to 252 ± 176.9 mL/min during cardiopulmonary bypass and remained higher than 170 mL/min for at least four hours in the postoperative unit. Patients who were given diuretics after 16 hours in the postoperative unit experienced increases in creatinine clearance, which lasted as long as six hours (increasing from 62 ± 28.0 mL/min before the diuretic to as high as 160 ± 114.8 mL/min at 22 hours in the postoperative unit). In no patient did renal dysfunction, persistent oliguria, or elevated serum creatinine levels (higher than the preoperative levels) develop.

Comment

Renal dysfunction was once common after cardiopulmonary bypass, occurring in 8% to 44% of patients, with frank renal failure in 2% to 13.5% during the 1960s and 1970s [1–7]. Clinical and laboratory studies from that era

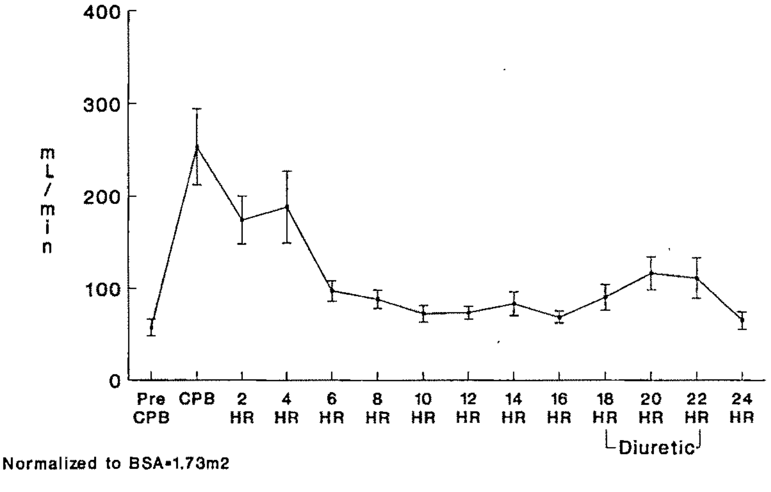

Fig 4. Creatinine clearance for the entire group. (Abbreviations are the same as in Figure 1.)

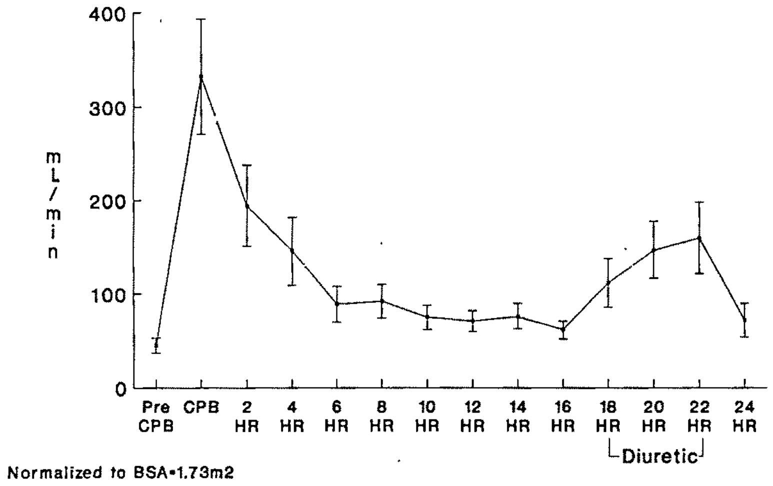

Fig 5. Creatinine clearance for the 9 patients requiring diuretics postoperatively. Creatinine clearance parallels urine output. (Abbreviations are the same as in Figure 1.)

confirmed the injurious effects of cardiopulmonary bypass on renal function [2–7, 9, 10]. However, the circumstances of cardiac surgery in its first two decades were much different from those of today. In the earlier experience, more patients underwent operation for valvular disease, many of whom had preexisting renal dysfunction, congestive heart failure, and low cardiac output. In addition, the techniques of anesthesia and cardiopulmonary bypass have changed: blood primes have been replaced by hemodilution, pump runs are shorter, and oxygenators have been improved. The fact that renal dysfunction and renal failure are now uncommon led us to examine, in serial fashion, changes in renal function before, during, and after cardiopulmonary bypass to see if earlier assumptions are still valid.

Mielke and colleagues [4], in a study published in 1966, found that 8 patients undergoing closure of an atrial septal defect all experienced anuria during the first half of cardiopulmonary bypass, with an abrupt increase to a mean urine output of 166 mL/h/1.73 m^2 (hemodilution) and 71 mL/h/1.73 m^2 (blood prime) during the latter portion of bypass. They concluded that the higher urine output in the hemodilution group resulted from an osmotic diuresis, which was thought to protect renal tubular integrity.

Porter and co-workers [2], in a study also published in 1966, studied 27 patients undergoing valve replacement. The creatinine clearances obtained during cardiopulmonary bypass were spuriously high. When the urine collections were fractionated into 30-minute intervals during cardiopulmonary bypass, the spuriously high clearance rates were traced to the first period. The authors thought that tubular secretion of creatinine continued independent of tubular flow rate, thus creating a tubular reservoir of creatinine that was available for excretion following the transition from low urine output before bypass to high urine output during cardiopulmonary bypass. This creatinine pool was exhausted within 30 minutes, after which time the urine to plasma creatinine ratios paralleled those for inulin and mannitol.

These findings are relevant to the present study in which the creatinine clearances (normalized to a body surface area of 1.73 m^2) during cardiopulmonary bypass averaged 252 mL/min, which may have been spuriously high. However, the fact that the tubular pool of creatinine is exhausted in 30 minutes indicates that our finding of high mean clearances after two and four hours in the postoperative unit (174 mL/min and 188 mL/min, respectively) was not artifactual and did, in fact, represent a sustained improvement in renal function.

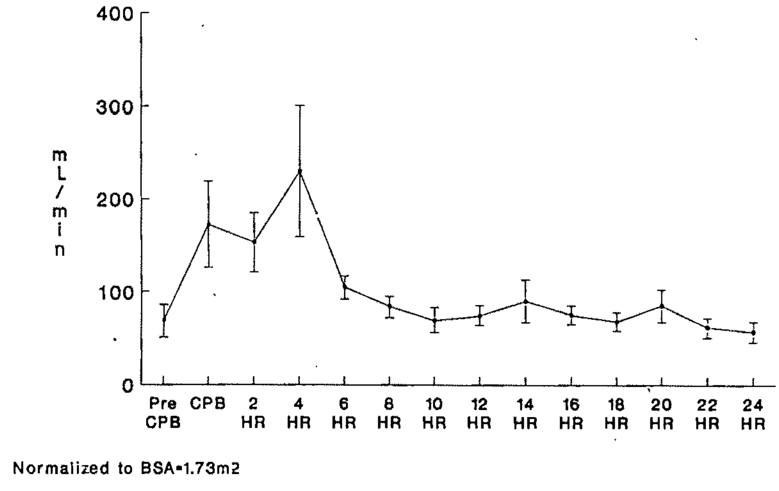

Fig 6. Creatinine clearance for the 9 patients who did not require diuretics. (Abbreviations are the same as in Figure 1.)

In a 1974 study of the effect of diuretics on renal hemodynamics in dogs, Engelman and co-workers [9] found that renal cortical flow decreased with or without a diuretic, but with furosemide, the decrease was significantly less. In 8 of 10 dogs in the nondiuretic group, renal cortical flow decreased to unmeasurable levels by 90 minutes. In the present study, furosemide was not used during cardiopulmonary bypass, but there were no instances of oliguria or decreased creatinine clearance. On the contrary, a sustained diuresis and improved creatinine clearance were present in every patient.

In a clinical study from 1976, Nuutinen and Hollmén [3] found that prophylactic use of furosemide improved renal function during prolonged cardiopulmonary bypass. However, it should be noted that they used a blood prime. Utley [1] proposed that hemodilution is probably the most important factor during cardiopulmonary bypass in protecting against renal damage. Hemodilution primes are now standard technique.

We used mannitol in our pump prime, but its contribution to improved renal function is uncertain. Yeboah and colleagues [6] thought that mannitol and furosemide, separately or together in a blood prime, had no influence on the incidence of renal failure in their patients. Utley and co-workers [10] stated that the effect of mannitol on glomerular and tubular function is not significant in the presence of hemodilution and hypothermic cardiopulmonary bypass.

In the postoperative period, furosemide and bumetanide proved to be effective in improving both urine output and creatinine clearance: patients given either of these diuretics after 18 hours in the postoperative unit had a sustained improvement in both urine output and creatinine clearance lasting four to six hours. This sustained improvement over several collection periods appears to rule out a tubular reservoir of creatinine as a cause of a spuriously high creatinine clearance.

In the late 1970s, there was considerable interest in improving renal function by providing pulsatile flow during cardiopulmonary bypass [11]. In the present study, renal function was well maintained despite use of a nonpulsatile system. It appears that present-day techniques of cardiopulmonary bypass preserve renal function without the addition of pulsatile perfusion.

One cause for concern is the low urine outputs noted in the operating room before cardiopulmonary bypass. In all likelihood, these low outputs were the result of preoperative dehydration. In patients with borderline renal function or in diabetics, it may be advisable to maintain intravenous hydration for the night before operation.

Contrary to previous experience, the present study indicates that modern techniques of cardiopulmonary bypass are not injurious to renal function. A sustained improvement in both urine output and creatinine clearance can be expected following cardiopulmonary bypass. Diuretics in the postoperative period improve both urine output and creatinine clearance for four to six hours. Low urine output just before operation is common and is probably the result of preoperative dehydration, which should be avoided in patients with borderline renal function.

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Reduction of Reperfusion Injury With Mannitol Cardioplegia

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Forty consecutive patients undergoing myocardial revascularization were divided into two equal groups: group 1 received standard cardioplegic solution, and group 2 received a solution containing mannitol, 59.8 mmol/L. In 6 patients in each group, myocardial biopsies were done before ischemia and at the time of reperfusion. Samples were assessed by chemiluminescence to determine oxidative stress and by electron microscopic studies. A significant reduction in atrial arrhythmias was observed in the mannitol group. Chemiluminescence in group 1 showed a photoemission of 37.6 ± 3.5 cpm/mg of protein × 10^{-3} for the preischemia samples and 74.8 ± 16 cpm/mg of protein × 10^{-3} for the reperfusion samples ($p < 0.001$). In group 2, the values for chemiluminescence were 37.7 ± 3.4 cpm/mg of protein × 10^{-3} and 40 ± 6.1 cpm/mg of protein × 10^{-3}, respectively (p = not significant). Electron microscopic studies showed, for group 1, increased grades of damaged mitochondria in the reperfusion biopsy specimens compared with the preischemia biopsy specimens ($p < 0.01$). In group 2, differences for damaged mitochondria were not significant. These results support the hypothesis that mannitol reperfusate significantly reduces myocardial damage in patients undergoing open heart procedures. They also suggest that this protective effect may be in part secondary to the antioxidant property of mannitol, although other mechanisms may have accounted for or contributed to the improved outcome after ischemia.

(Ann Thorac Surg 1989;48:77–84)

Although topical cooling and cold potassium cardioplegia have markedly reduced mortality and morbidity in open heart procedures, there still exists a variable degree of myocardial injury as a consequence of the ischemia/reperfusion mechanism. Cell damage has been assessed by both ultrastructural and histochemical studies, and is clinically expressed by the presence of disturbances in the conduction system and supraventricular and ventricular arrhythmias. Moreover, in patients with a low ejection fraction preoperatively, the postoperative period can also be associated with impaired ventricular function.

Evidence accumulated over the past several years indicates that oxygen-derived free radicals are in part responsible for the production of reperfusion injury. We [1] have recently observed the presence of myocardial oxidative stress caused by these metabolites in patients who underwent coronary artery bypass grafting. It has also been shown in animal models [2–5] that a variety of antioxidants or scavengers are able to reduce cell damage associated with the ischemia/reperfusion mechanism as well as the incidence of reperfusion-induced arrhythmias. Moreover, proarrhythmic effects were obtained when the heart was exposed to an oxygen-derived free radical–generating system [5].

In the present study, we tested the hypothesis that administration of mannitol in a cardioplegic solution reduces the incidence of postoperative arrhythmias and myocardial damage. Oxygen free radical activity was indirectly assessed by chemiluminescence and myocardial damage, by electron microscopic studies.

Material and Methods

This prospective trial involved 40 patients who underwent coronary artery bypass grafting between September 1, 1987, and February 1, 1988. To obtain a homogeneous group, patients with the following characteristics were considered for the study: an ejection fraction greater than 45%; absence of recent (less than 4 weeks) myocardial infarction; and complete or satisfactory revascularization at the time of operation. The patients were divided into two equal groups based on the cardioplegic solution used. Age, ejection fraction, aortic-cross clamp time, and number of grafts performed were similar in the two patient groups (Table 1). Written informed consent was obtained from those patients who were selected for myocardial biopsy.

Cardiopulmonary bypass was instituted, and the perfusate was cooled to 28°C. Topical hypothermia with crushed ice saline solution was added. The two study groups were as follows: 20 patients (group 1) received 500 mL of standard cardioplegic solution, and 20 patients (group 2) received 500 mL of a cardioplegic solution containing mannitol (59.8 mmol/L) (Laboratorios FADA, Buenos Aires, Argentina). The composition of the infu-

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Table 1. Characteristics of the Two Groups[a]

Variable	Group 1, Control (n = 20)	Group 2, Mannitol (n = 20)
Age (yr)	52.4 ± 2	53.8 ± 2
Ejection fraction (%)	53 ± 2	53.2 ± 3
Aortic cross-clamp time (min)	48.2 ± 3	53.8 ± 2
No. of grafts	2.8 ± 0.2	3 ± 0.2
LAD grafts	17	18

[a] Data are shown as the mean ± the standard error of the mean where applicable.

LAD = left anterior descending coronary artery.

sions is listed in Table 2. The osmolarity of both perfusates was measured with a vapor pressure osmometer (Wescor 5500, Wescor, Logan, UT).

In both groups the solution was administered into the aortic root at a temperature of 4°C and a pressure ranging between 80 and 100 mm Hg. A needle thermistor (Yellow Springs Instrument Company, Yellow Springs, OH) was inserted into the septum for continuous monitoring of myocardial temperature, which was maintained at approximately 18°C. After each distal anastomosis was constructed, 50 mL of the respective cardioplegic solution was given into the vein graft. In all circumstances, at least one of the internal mammary arteries was used, and this anastomosis was done as the last step before the aortic clamp was removed.

Six patients in each group were randomly chosen to undergo myocardial biopsies, which were done according to the following protocol. Before the aorta was cross-clamped, full-thickness needle biopsy specimens (Travenol Tru-cut biopsy needle) were obtained from the apex of the left ventricle. Specimens for chemiluminescence determination were immersed in normal saline solution and immediately frozen, and specimens for electron microscopy were placed in cold 3% glutaraldehyde in 0.1 mol/L of cacodylate buffer (pH 7.4). Both sets of specimens were designated as preischemia samples. After completion of the distal anastomoses, the aortic cross-clamp was removed and defibrillation was performed at 30° to 33°C using a 40–W-s direct-current countershock. After ten minutes of reperfusion and with the patient rewarmed, new biopsy specimens were obtained and processed as described. These specimens were designated as reperfusion samples. The patient was weaned from cardiopulmonary bypass when the systemic temperature reached 37°C.

Study of Rhythm Disturbances

At the time of operation, the number of electric countershocks required to defibrillate the heart after the aortic cross-clamp was removed was registered. Rhythm disturbances that occurred within the first 24 hours after operation and required treatment were considered. They included the following: atrial fibrillation; supraventricular tachycardia, defined as six or more consecutive premature supraventricular complexes with a frequency greater than 100 beats per minute; ventricular tachycardia, defined as six or more consecutive premature ventricular complexes with a frequency greater than 100 beats per minute; frequent premature ventricular complexes, defined as 30 or more premature ventricular complexes per hour; and second-degree or third-degree atrioventricular block. Personnel of the intensive care unit were specially advised to continuously observe and register the type and frequency of rhythm disturbances appearing on a telemetric monitor.

Hydroperoxide-Initiated Chemiluminescence

Frozen biopsy specimens (approximate weight, 20 mg) were placed in saline solution at 0° to 2°C and rushed to the laboratory. The samples were homogenized in a small Potter Elvejhem Teflon homogenizer in 120 mmol/L of KCl and 30 mmol/L of phosphate buffer (pH 7.5) at 0° to 2°C. The homogenate was warmed to 30°C, combined with 3 mmol/L of tert-butyl hydroperoxide, and assayed for chemiluminescence in a Packard Tri-Carb model 3320 scintillation counter (Packard Instrument Co, Santa Ana, CA) in the out-of-coincidence mode [6, 7]. The proteins of the homogenate were determined by the method of Lowry and associates [8], and chemiluminescence was expressed as counts per minute per milligram of homogenate protein. Determinations were conducted in a blind manner by two different observers.

Electron Microscopy

Tissues for transmission electron microscopy were fixed in cold 3% glutaraldehyde in 0.1 mol/L of cacodylate buffer (pH 7.4), postfixed in 1% osmium tetroxide, dehydrated, and embedded in Epon. Three blocks were selected from different depths of the biopsy specimen, and from each block, a section 1 μm thick was cut, stained with 1% toluidine-borax, and examined by light microscopy to select appropriate areas for thin sectioning. Five ultrathin sections were obtained from each of the three blocks. Ultrathin sections mounted in copper grids were stained with uranyl acetate and lead citrate and examined with a Siemens Elmiskop 1A electron microscope.

Electron micrographs were systematically taken at

Table 2. Composition of the Two Cardioplegic Solutions

Variable	Standard	Mannitol
Dextrose (mmol/L)	14	28
NaCl (mmol/L)	154	90.7
KCl (mmol/L)	20	33
CaCl (mmol/L)	1.2	0.54
MgCl (mmol/L)	16	. . .
$NaHCO_3$	10	. . .
Mannitol (mmol/L)	. . .	59.8
Glycine (mmol/L)	. . .	49
pH at 5°C	7.8	7.8
Osmolarity (mosm/L)	380	360

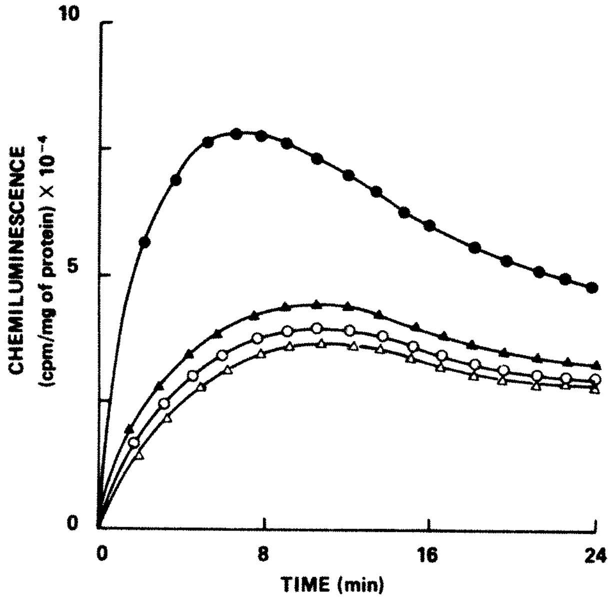

Fig 1. Time course of hydroperoxide-initiated chemiluminescence shows the effect of mannitol reperfusate in the reperfusion samples from group 2. (▲ = group 1 preischemic samples; ● = group 1 reperfusion samples; △ = group 2 preischemia samples; ○ = group 2 reperfusion samples.)

×2,500 and ×10,000 magnification for the comparative evaluation of the preischemia and reperfusion samples in both groups. A single score was given for each area, and the observations were conducted in a blind manner by two different observers. According to the criteria of Kloner and co-workers [9], the severity of mitochondrial swelling was graded 0 through 4 as follows: 0 = normal mitochondria; 1 = early swelling as manifested by separation of cristae and clearing of matrix density; 2 = more marked swelling than in grade 1; 3 = massive swelling with architectural disruption; and 4 = the findings in grade 3 plus rupture of inner and outer mitochondrial membranes.

When a point on the grid fell on a mitochondrion, this mitochondrion was assigned a numerical value of 0 through 4 depending on its morphological degree of damage. A mean mitochondrial grade for each cell was obtained by calculating the weighted average (0 through 4) of mitochondrial swelling. Approximately 200 mitochondria per sample were graded in this manner.

Statistical Analysis

The paired *t* test was used to determine the significance of differences, and data were expressed as the mean ± the standard error of the mean. Data from chemiluminescence were analyzed by variance factorial design. To compare the incidence of rhythm disturbances in the two groups, the χ^2 test was used.

Results

Clinical Outcome

All patients recovered satisfactorily from the operation. There were no perioperative myocardial infarctions as measured by the appearance of new Q waves on the electrocardiogram or by increased values for serum creatine kinase. Four patients in group 1 and 3 in group 2 required inotropic support four to 18 hours after operation. No patient required a major dose of dopamine hydrochloride (more than 5 μg/kg/min). The hospital mortality was 2.5%; 1 patient in group 1 had uncontrolled gastrointestinal bleeding and died on the 13th postoperative day.

Rhythm Disturbances

The number of countershocks needed to reverse ventricular fibrillation at the time of reperfusion was 1.7 ± 0.4 in group 1 and 1.0 ± 0.27 in group 2 ($p < 0.02$). Rhythm disturbances developed in 7 patients (35%) in group 1: atrial fibrillation in 3, frequent premature ventricular

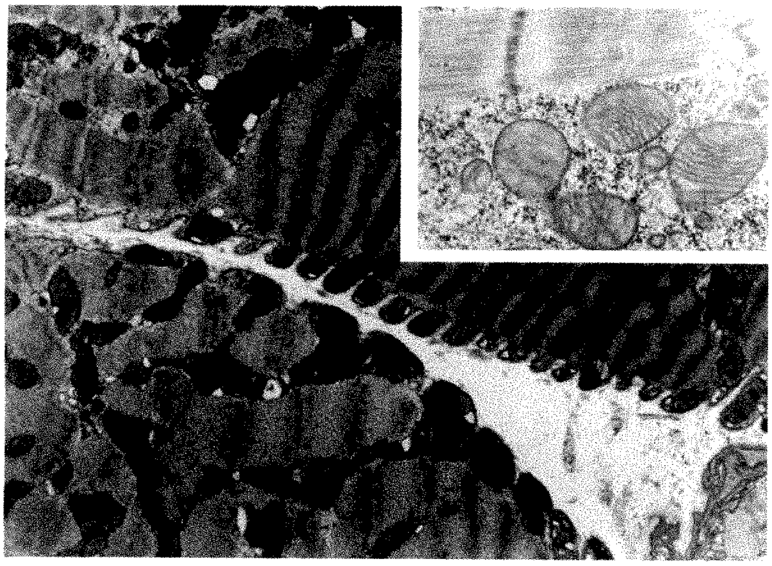

Fig 2. Electron micrograph of preischemia biopsy specimen demonstrates preserved architecture of the sarcomere. The mitochondria have intact membranes and tightly packed cristae. (×25,000 before 38% reduction.) Inset shows that mitochondria and sarcomere both have a normal appearance. (×20,000 before 38% reduction.)

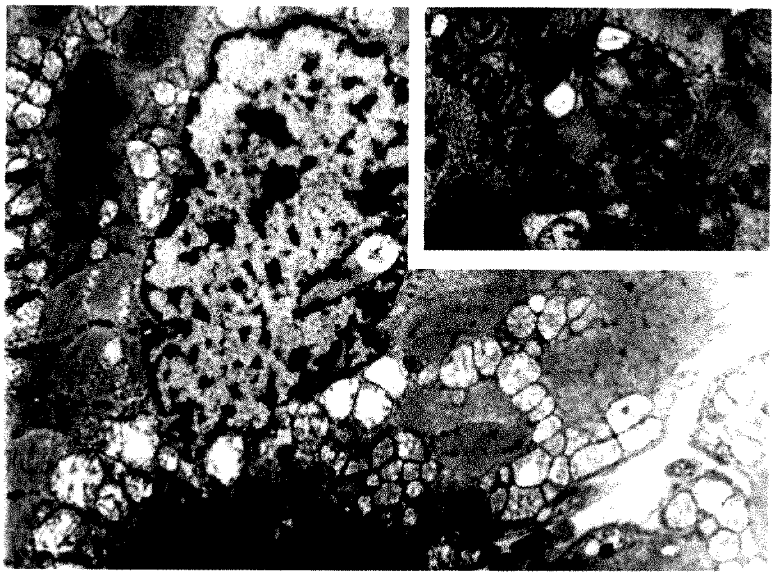

Fig 3. Electron micrograph of reperfusion biopsy specimen from a patient in group 1 shows areas of focal myofibrillar disorganization with myocytolysis. Mitochondria demonstrate slight to moderate edema, and in some areas, there is clarification of the matrix with massive swelling (arrow). *(×25,000 before 38% reduction.) Inset shows mitochondria with moderate swelling. (×10,000 before 38% reduction.)*

complexes in 2, supraventricular tachycardia in 1, and transient third-degree atrioventricular block in 1. In group 2, 1 patient (5%) had transient third-degree atrioventricular block. This difference was significant ($p < 0.05$).

Hydroperoxide-Initiated Chemiluminescence

The mean value for hydroperoxide-initiated chemiluminescence in the preischemia biopsy specimens from the 6 group 1 patients was 37.6 ± 3.5 cpm/mg of protein $\times 10^{-3}$ and in the reperfusion biopsy specimens, 74.8 ± 16 cpm/mg of protein $\times 10^{-3}$. In group 2, the photoemission count for the preischemia biopsy specimens was 37.7 ± 3.4 cpm/mg of protein $\times 10^{-3}$ and for the reperfusion specimens, 40 ± 6.1 cpm/mg of protein $\times 10^{-3}$. The photoemission count was significantly reduced in the reperfusion biopsy specimens from group 2 compared with those from group 1 ($p < 0.001$). No significant differences were found between the preischemia samples from both groups or between the preischemia and postischemia samples from group 2. Figure 1 shows the markedly increased hydroperoxide-initiated chemiluminescence in the reperfusion samples from group 1 compared with those from group 2.

Electron Microscopy

QUALITATIVE ANALYSIS. The preischemia biopsy specimens from both groups showed well-preserved intercalated discs and similar mitochondrial arrangement, density, and general morphology. The cytoplasmic myofilament, glycogen, and sarcolemma were well preserved (Fig 2). Morphological changes in the reperfusion biopsy specimens from group 1 showed areas of focal myo-

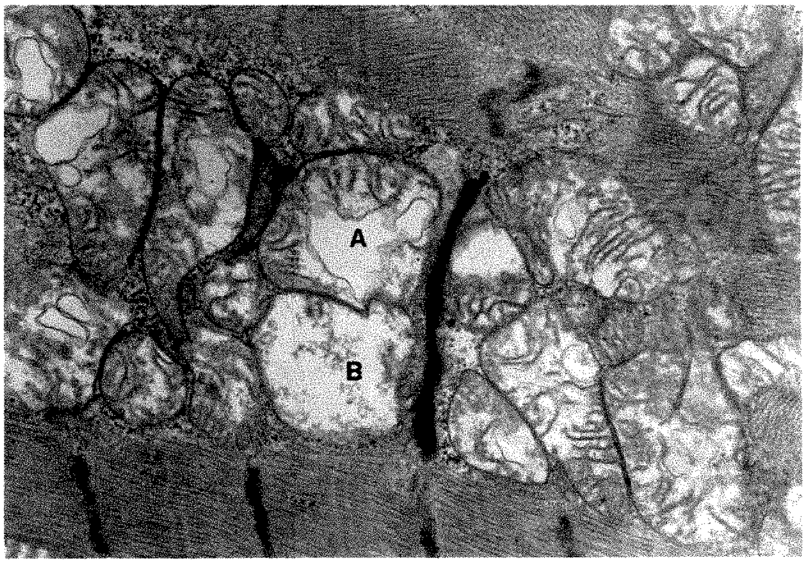

Fig 4. Electron micrograph of reperfusion biopsy specimen from a patient in group 1: details of an area showing (A) *severe damage of mitochondria with massive swelling and disruption of cristae and* (B) *mitochondria with marked swelling and rupture of membranes. (×20,000 before 38% reduction.)*

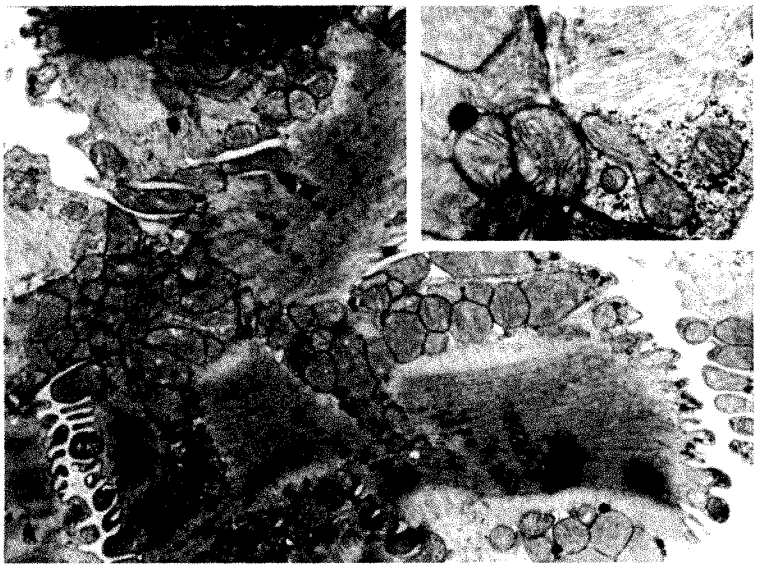

Fig 5. Electron micrograph of reperfusion biopsy specimen from a patient in group 2. The cytoplasmic myofilaments and sarcolemma are well preserved. The mitochondrial arrangement is similar to the preischemia biopsy specimen. (×2,500 before 38% reduction.) Inset shows mitochondria with normal arrangement of the matrix and minimal edema. (×20,000 before 38% reduction.)

fibrillar disorganization with myocytolysis and sarcoplasmic vacuolation. Mitochondria had minimal to moderate swelling in some myocardial areas (Fig 3) and massive swelling and disrupted cristae in others (Fig 4). Reperfusion biopsy specimens from group 2 showed mitochondria with well-preserved architecture, tightly packed cristae, and gray matrix density in most of the electron micrographs. In some scattered areas, moderate swelling with clearing of matrix density and separation of cristae was observed, but no abnormalities of myofibrillar organization were detected (Fig 5).

QUANTITATIVE ANALYSIS. In group 1, the percentage of severely damaged mitochondria, grades 3 and 4, was 6% ± 2% and 5% ± 2%, respectively, for the preischemia samples. For the reperfusion samples, grades 3 and 4 were 16% ± 5% and 15% ± 2%, respectively. These results were significantly different for grade 4 ($p < 0.05$) (Table 3). Values for normal (grade 0) mitochondria in the same group were significantly different when the preischemia and reperfusion samples were compared ($p < 0.05$). In group 2, similar values were observed in both the preischemia and reperfusion samples (see Table 3).

Comment

Our study shows that the addition of mannitol to a cardioplegic solution significantly decreased the number of countershocks required to return the heart to sinus rhythm. Also observed was a reduction in rhythm disturbances during the first 24 postoperative hours. In this respect, the complete disappearance of atrial fibrillation was remarkable in the mannitol group (group 2). Furthermore, our study suggests that mannitol or the potentiation effect of mannitol by glucose may reduce the occurrence of oxidative stress as shown by a marked decrease in the hydroperoxide-initiated chemiluminescence in the biopsy specimens of group 2. Similarly, a relatively pre-

Table 3. Grading of Mitochondrial Damage[a]

Group	Sample[b]	Mitochondrial Grade (%)					No. of Mitochondria Checked
		0	1	2	3	4	
1 (n = 6)	A	60 ± 9	16 ± 5	13 ± 3	6 ± 2	5 ± 2	209 ± 17
	B	36 ± 7	17 ± 2	16 ± 3	16 ± 5	15 ± 2	194 ± 8
p Value		<0.05	NS	NS	NS	<0.01	NS
2 (n = 6)	A	69 ± 12	12 ± 3	9 ± 4	5 ± 3	5 ± 2	231 ± 16
	B	60 ± 4	16 ± 2	11 ± 4	6 ± 1	7 ± 1	202 ± 17
p Value		NS	NS	NS	NS	NS	NS

[a] Data are shown as the mean ± the standard error of the mean. [b] A represents the samples obtained before ischemia and B, those obtained after 10 minutes of reperfusion.

NS = not significant.

served ultrastructure, as shown by the morphometric analysis of electron micrographs, was characteristic of the mannitol biopsy specimens. To our knowledge, this is the first study of these properties of mannitol in humans.

Hydroperoxide-initiated chemiluminescence constitutes a reliable method within the various techniques currently used for determining oxidative stress [10, 11]. This assay appears to have a higher degree of sensitivity than malondialdehyde formation. Hydroperoxide-initiated chemiluminescence has been used to detect decreased levels of endogenous antioxidants in brain and liver homogenates from ethanol-treated rats [12] and from tumor-bearing mice [13] and in heart homogenates from Adriamycin (doxorubicin hydrochloride)-treated rabbits and mice [14, 15].

In this decade, considerable interest has arisen over the role of oxygen-derived free radicals in reperfusion-induced damage of the heart, and within this field, some investigators [2–5] focused their research on the implication of free radicals in the genesis of reperfusion-induced arrhythmias. These authors have shown the arrhythmogenic properties of an oxygen-derived free radical–generating system. They have also demonstrated that the addition of antioxidant agents such as superoxide dismutase, catalase, mannitol, glutathione, or desferrioxamine in the perfusion medium exerts an antiarrhythmic effect in the isolated animal heart subjected to regional ischemia and reperfusion.

Oxygen free radicals, particularly the $OH^\cdot$, attack unsaturated fatty acid chains and other cell structures such as proteins and deoxyribonucleic acid. Because unsaturated fatty acids are in abundance in cell membranes, they become critical targets of free radical activity, and a propagation reaction (lipoperoxidation) is initiated [16].

The mechanism by which oxygen free radicals are generated on reperfusion remains unclear. The role of xanthine oxidase as a source of these metabolites has been observed in animals, but, as reported in 1986 [17], the human heart has little if any xanthine oxidase activity; therefore the hypothesis that xanthine oxidase catalyzes the generation of the superoxide anion ($O_2^\cdot$) may not be applied in the clinical setting.

In the alternative hypothesis, on reperfusion, oxygen encounters a highly reduced mitochondrial respiratory chain, which triggers a high production of $O_2^\cdot$ at the inner mitochondrial membrane [18]. After dismutation of $O_2^\cdot$ at the mitochondrial matrix, the resulting H_2O_2 diffuses out of the cytosol, reacts with myoglobin, and produces $HO^\cdot$ [19].

In a previous work, we [1] showed that in patients undergoing myocardial revascularization, a burst of oxygen free radicals is generated on reperfusion, and this was demonstrated by a significant rise in hydroperoxide-initiated chemiluminescence. This was associated with cell damage assessed both by ultrastructural studies and by the determination of histochemical succinic dehydrogenase activity. Encouraged by these results, we tested in the present study the hypothesis that the addition of mannitol to the cardioplegic solution would offer better protection to the heart.

Mannitol has been shown to improve myocardial function after ischemia. One possible mechanism of action is related to its osmotic activity, decreasing cellular edema by creating a hyperosmotic extracellular milieu. Magovern and co-workers [20] tried to elucidate the mechanisms by which reperfusion with mannitol is beneficial. They reperfused rabbit hearts with two equally hyperosmotic solutions, one containing mannitol and the other containing glucose. The mannitol group demonstrated a better tolerance to ischemia on the basis of ventricular function determinations, measurement of coronary flow, and myocardial edema formation. These results provided suggestive evidence that mannitol may achieve a myocardial protective effect by some other property than its hyperosmotic action. These authors hypothesized that mannitol could act as a scavenger of free radicals. It has been reported [21] that mannitol is an oxygen free radical scavenger of the OH by forming a mannitol radical ($MH2 + OH^\cdot \rightarrow MH^\cdot + H_2O$) that undergoes disproportionation or dimerizes.

The standard cardioplegic solution in our experience possesses higher osmolarity than the mannitol solution. Therefore the better preservation of ultrastructure observed in the mannitol samples should be explained by mechanisms other than hyperosmolarity. Another aspect that must be taken into consideration is the determination of the optimal concentration of mannitol in a cardioplegic solution. Bernier and associates [4] found effective reduction of ventricular fibrillation with 50 mmol/L of mannitol, and recently the same group [22] observed the potentiation of the antifibrillatory effects of mannitol (50 mmol/L) by low concentrations (11 mmol/L) of glucose. The mechanism for this effect remains to be elucidated.

We introduced chemiluminescence as an indirect method to assess free radical activity, and a significant reduction in photoemission was observed in the biopsy specimens from the mannitol group. Our results suggest that the protective action of mannitol or the interaction of mannitol and glucose is in part secondary to a scavenging property. However, we concede that several aspects remain unclear. Is mannitol limited to the vascular space under these conditions, whether simply by membrane permeability factors or by reduced mannitol diffusion because of hypothermia? Or is it conceivable that with ischemia, there are sufficient increases of sarcolemmal permeability to allow the relatively small mannitol molecule to gain access to the cytosol? If mannitol could diffuse in amounts sufficient to reach an effective scavenging concentration within the cells, then it could be acting through the ascribed mechanism. The role of activated leukocytes as an oxidant source is also well known. In spite of the washout effect of the perfusate, an undetermined number of leukocytes reach the capillary system of the myocardium through the noncoronary flow, and mannitol may act over the free radicals generated by these cells. Further investigations are necessary to clarify the mechanisms by which antioxidant agents including mannitol exert their protective action when administered in a cardioplegic solution.

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INVITED COMMENTARY

This article by Ferreira and colleagues is provocative and potentially important. However, there are several caveats in its interpretation. First, patients were randomized to one of two treatment groups without informed consent. The rationale was that mannitol is commonly used in cardioplegic solutions anyway, and informed consent was, therefore, unnecessary. Moreover, it was not required by the local institutional review board. While not disagreeing with this contention, an important principle of human research is that when treatment is assigned, strictly on the basis of study participation, consent must be obtained. Responsibility for enforcement is both that of the authors and that of *The Annals.*

Second, the occurrence of increased chemiluminescence in biopsy specimens from patients treated with mannitol is not specific for the occurrence of free radical moieties. For example, changes in the redox state of tissue iron can influence chemiluminescence. Moreover, using the current study design, no evidence is provided that the simple presence of mannitol in the myocardial tissues did not influence chemiluminescence. It is of interest that the extent of chemiluminescence did not correlate with the duration of aortic cross-clamp time; most hypotheses of free radical injury suggest that the extent of this phenomenon should relate directly to the extent of ischemic injury.

Third, the potential dangers of subjecting a small sampling of the patient population to biopsy introduces statistical hazards not present when the biopsy technique is applied to greater numbers of the studied population.

Fourth, side-by-side comparison of the two cardioplegic solutions reveals differences not limited to the inclusion of mannitol. Differences exist in four other components of the solution that cannot be excluded as contributing to the results. The sodium chloride concentration in the mannitol-containing cardioplegic solution was about 60% of that in the standard solution, the potassium chloride concentration was 50% greater in the mannitol solution, the calcium chloride concentration in the standard solution was half the concentration in the mannitol solution, and the standard solution contained 16 mmol/L of magnesium chloride, whereas none was present in the mannitol-containing solution. These are not inconsequential differences and must be kept in mind when interpreting the data.

Despite these concerns, Ferreira and colleagues are to be complimented for attempting to use the operating room laboratory to assess scientifically important issues. The data generated, however, should not lead any practicing surgeon to include mannitol in the cardioplegic solution without further evidence of benefit.

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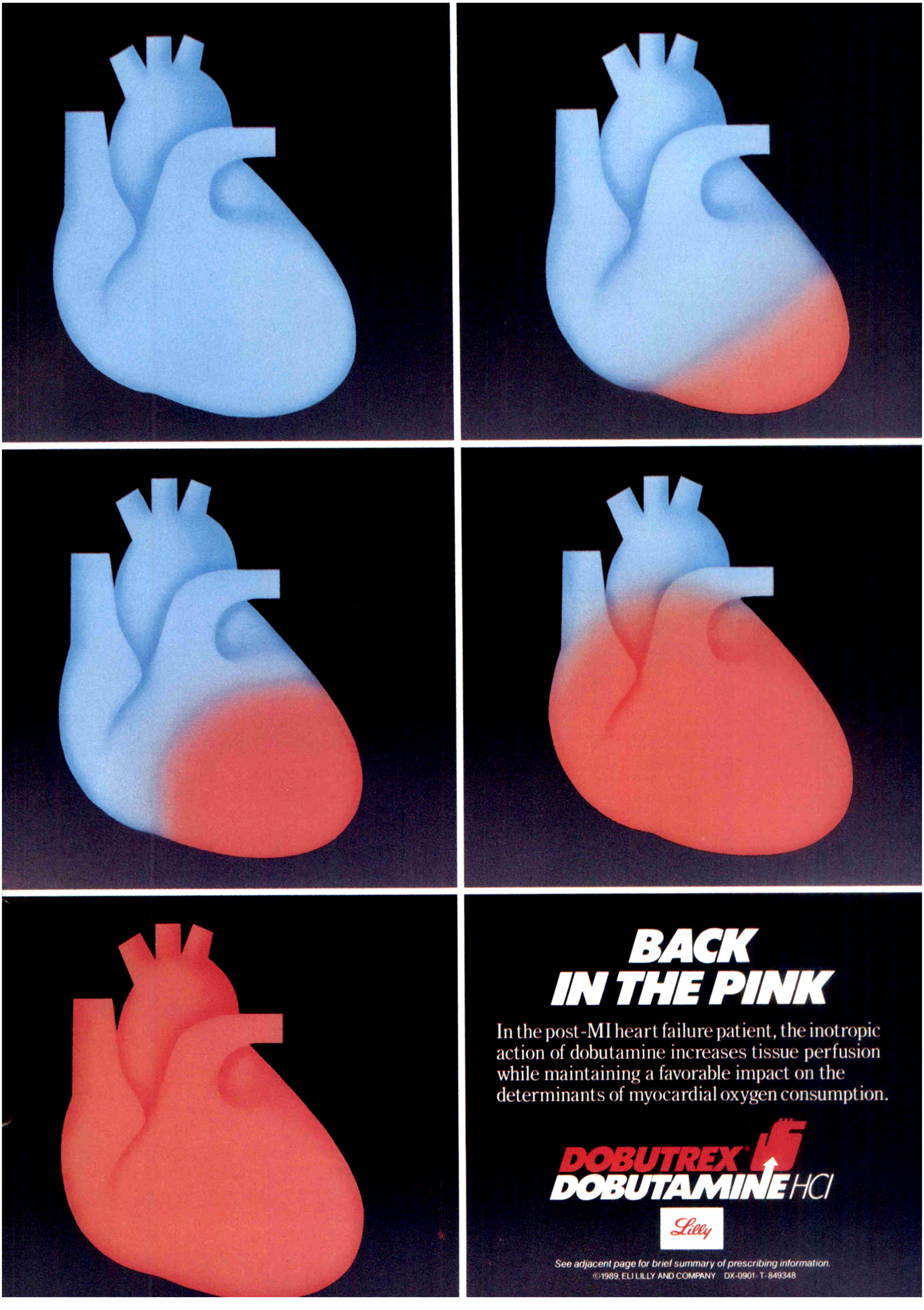
Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the cardiothoracic operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1991 may begin the recertification process in 1989. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1989. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.



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Excessive dosages of Dobutrex or other inotropic agents may produce unwanted alterations in blood pressure, heart rate, or ventricular ectopic activity.

Brief Summary. Consult the package literature for prescribing information.

Clinical Pharmacology: Dobutrex Solution is a direct-acting inotropic agent whose primary activity results from stimulation of the ß-receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short term—not more than several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas output returned toward baseline values in others.

The onset of action of Dobutrex Solution is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

Indications and Usage: Dobutrex Solution is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex Solution.

Contraindications: Dobutrex Solution is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to Dobutrex Solution.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex Solution may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Usually, reduction of dosage reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex Solution may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

3. *Hypersensitivity*—Reactions suggestive of hypersensitivity associated with administration of Dobutrex Solution, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

4. Dobutrex Solution contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Precautions: 1. During the administration of Dobutrex Solution, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex Solution.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex Solution is instituted.

3. Animal studies indicate that dobutamine may be ineffective if the patient has recently received a ß-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex Solution following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent that increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex Solution for use in children have not been studied.

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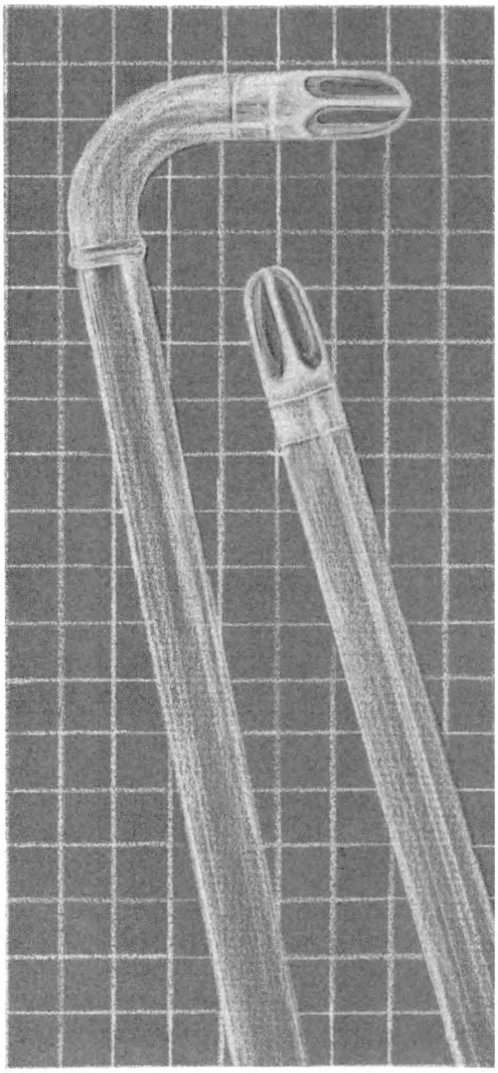

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Coronary Artery Bypass Grafting in Patients With Ventricular Fibrillation

Irving L. Kron, MD, Bruce B. Lerman, MD, David E. Haines, MD,
Terry L. Flanagan, MPH, and John P. DiMarco, MD, PhD

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The role of coronary artery revascularization in the management of survivors of cardiac arrest remains controversial. Patients with sustained monomorphic ventricular tachycardia rarely respond to revascularization, but the response of patients with ventricular fibrillation as their basic arrhythmia has not been characterized. Coronary artery bypass grafting was performed in 8 patients with a history of cardiac arrest known to be caused by ventricular fibrillation without preceding sustained monomorphic ventricular tachycardia. All patients had critical double-vessel or triple-vessel coronary artery disease, and 7 of 8 had wall motion abnormalities from a prior myocardial infarction. After successful operation, 5 patients had no spontaneous arrhythmias and no inducible arrhythmias at a postoperative electrophysiological study. Three patients, however, had spontaneous, recurrent episodes of ventricular fibrillation unassociated with recurrent ischemia. Clinical factors were not useful predictors of response. The effect of coronary artery revascularization in patients with ventricular fibrillation is unpredictable, and full postoperative electrophysiological evaluation is necessary to judge the success of the procedure.

(Ann Thorac Surg 1989;48:85–9)

Monomorphic ventricular tachycardia is an arrhythmia whose site of origin can often be electrophysiologically mapped and then surgically ablated. In recent series, several groups [1–4] have documented surgical success rates of 70% to 90% for patients with monomorphic ventricular tachycardia. The surgical approach in patients with cardiac arrest and ventricular fibrillation is less well defined. Ventricular fibrillation at the time of resuscitation may have been preceded by a period of monomorphic ventricular tachycardia and if monomorphic ventricular tachycardia is inducible at electrophysiological study, these patients can be managed by the usual techniques.

In many patients, however, monomorphic ventricular tachycardia is not induced at electrophysiological study, and either rapid, polymorphic ventricular tachycardia or ventricular fibrillation is the only arrhythmia observed [5, 6]. These arrhythmias cannot be mapped to a single, discrete site of origin, and some authors [7] have postulated that, at least in patients with coronary artery disease, ischemia is the underlying cause of the arrhythmia. To evaluate this hypothesis, we have retrospectively reviewed preoperative and postoperative clinical and electrophysiological data from 8 patients who were seen with ventricular fibrillation and then subsequently underwent coronary artery revascularization.

Material and Methods

Patient Population

Eight patients with a documented history of cardiac arrest and ventricular fibrillation without preceding monomorphic ventricular tachycardia underwent coronary artery bypass grafting without myocardial resection or ablation between 1983 and 1988 at the University of Virginia Hospital. Patients who had ventricular fibrillation only within the first 48 hours after myocardial infarction were not eligible for inclusion. The onset of ventricular fibrillation without preceding monomorphic ventricular tachycardia was documented by electrocardiographic monitoring (3 patients), a preoperative electrophysiological study (1 patient), or both methods (4 patients).

Preoperative Evaluation

All patients underwent coronary arteriography and biplane left ventriculography using standard techniques. In 3 patients, the presence of either a critical left main coronary artery lesion or progressive chest pain led to a clinical diagnosis by the original physician of ischemia as the cause of ventricular fibrillation, and preoperative electrophysiological studies were not performed. The remaining 5 patients underwent a preoperative electrophysiological study after discontinuation of any prior antiarrhythmic drug therapy using methods previously described [2]. In brief, the stimulation protocol used in our laboratory includes routine assessment of sinus node function and atrioventricular conduction and programmed ventricular stimulation with up to three extrastimuli from up to two right ventricular sites [8]. Standard definitions for electrophysiological findings were used [9]. Only sustained (>30 seconds) ventricular arrhythmias

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were considered clinically significant responses to stimulation.

Coronary artery bypass grafting was carried out using moderate hypothermia and crystalloid cardioplegia. Grafts were placed to all major vessels with stenosis of greater than 50% angiographically except one, a right coronary artery in patient 7 that was too severely diseased to accept a graft.

Patients without spontaneous clinical arrhythmias during the postoperative period underwent repeat electrophysiological study using the ventricular stimulation protocol already described. Patients with ventricular tachycardia or ventricular fibrillation at the postoperative electrophysiological study had therapy guided by serial electrophysiological studies.

Results

Patient Profile

The study group included 6 men and 2 women with a mean age of 63 ± 4 years (Table 1). The mean left ventricular ejection fraction was 39% ± 13% with 7 of the 8 patients having one or more regional areas of akinesia or dyskinesia. No patient had only a single discrete thin-walled aneurysmal segment. One patient had no major wall motion abnormalities on left ventriculography. Three patients had greater than 70% stenosis in two coronary vessels, while 5 patients had major triple-vessel disease. Four patients were seen initially with progressive angina and had ventricular fibrillation during attempted in-hospital medical therapy, and 4 patients were seen initially with an unexpected out-of-hospital cardiac arrest. No patient was on a regimen of antiarrhythmic drug therapy at the time of arrest. Three patients had multiple episodes of ventricular fibrillation; only a single episode occurred in the remaining 5.

Preoperative Electrophysiological Findings

Preoperative electrophysiological studies were not performed in 2 patients because of unstable angina and in 1 patient with multiple arrests and a 95% stenosis in the proximal left main coronary artery. Sustained ventricular fibrillation not preceded by monomorphic ventricular tachycardia was inducible in all 5 patients undergoing preoperative electrophysiological studies. The induction of ventricular fibrillation required two extrastimuli in 4 patients and three extrastimuli in 1 patient. Because no mappable arrhythmia had ever been documented in any patient, intraoperative electrophysiological studies were not performed. No patient sustained a perioperative myocardial infarction.

Postoperative Findings

Three patients (patients 5, 7, 8) had spontaneous episodes of ventricular fibrillation 4, 5, and 5 days postoperatively. One patient (patient 5) could not be resuscitated. At autopsy, all three of the grafts were patent, and no evidence of a perioperative myocardial infarction was found. The other 2 patients with spontaneous postoperative ventricular fibrillation had patency of all grafts documented at repeat coronary angiography.

All patients with the exception of patient 5 underwent repeat electrophysiological study nine ± two days after operation. Both patients resuscitated after spontaneous postoperative ventricular fibrillation had ventricular fibrillation induced by programmed electrical stimulation. Both were eventually managed with antiarrhythmic drug therapy with amiodarone. The other 5 patients had no inducible ventricular arrhythmia after operation.

The presence of preoperative unstable angina was not a useful predictor of a successful electrophysiological outcome after coronary artery bypass. Two of 4 patients with and 3 of 4 patients without unstable angina preoperatively had control of spontaneous or inducible ventricular fibrillation or both. All three failures occurred in the group of 7 patients who had wall motion abnormalities due to prior myocardial infarction; the single patient with normal left ventricular function and no history of infarction had no inducible arrhythmias at the postoperative study.

Follow-up

Seven of the 8 patients survived to hospital discharge. Two received long-term antiarrhythmic drug therapy as described. During the follow-up of 23 ± 19 months, 1 patient has died of refractory congestive heart failure and recurrent pulmonary edema. The remaining 6 patients are alive and well without arrhythmia recurrence.

Comment

The role of coronary artery revascularization in the management of life-threatening ventricular arrhythmias has been controversial. Recurrent monomorphic ventricular tachycardia only rarely is controlled by myocardial revascularization, and direct excision or ablation of the tissue responsible for the tachycardia is required [10]. Ventricular fibrillation is not, however, a mappable arrhythmia as usually defined, and some authors [7, 11] have proposed that it be considered a marker for myocardial ischemia.

Older studies on the effects of coronary artery bypass grafting on ventricular arrhythmias often focused on patients with nonsustained or exercise-induced ventricular ectopia. Weiner and colleagues [12] showed that ventricular ectopia persisted after coronary artery bypass in patients with either fixed wall-motion abnormalities or residual ischemia. Lehrman and co-workers [13] also found no effect of bypass procedures on exercise-induced arrhythmias in their long-term study.

In contrast, other studies have suggested that coronary artery bypass grafting may prevent sudden death. In an early study, Myerburg and associates [14] reported that 8 patients with aborted sudden death survived long term after revascularization. Tresch and co-authors [15] described a decreased mortality after revascularization in a select group of survivors of sudden death. In the Coronary Artery Surgery Study (CASS) [16], coronary bypass procedures decreased the mortality due to sudden death, particularly in patients with triple-vessel coronary artery disease and left ventricular dysfunction. In contrast to these reports, however, we [17] and others [18] have noted that first episodes of sustained ventricular tachycardia or ventricular fibrillation can occur early after an

Table 1. Summary of Patient Data

Patient No.	Age (yr)	Sex	Symptoms Prior to Arrest	No. of Episodes of VF	Left Ventricular Ejection Fraction (%)	Wall Motion Abnormalities	Coronary Arteries With >70% Stenosis	No. of Bypass Grafts	Electrophysiological Findings		Drug Therapy	Outcome
									Preop	Postop		
1	58	F	None	10	23	Anterolateral, septal, posterolateral	Left main, LCFx, right	3	Not done	No VT at EPS	None	Alive and well at 36 mo
2	68	M	Syncope	1	24	Anteroseptal, posterolateral	LAD, LCFx, right	3	VF (2 ES)	No VT/VF at EPS	None	Alive and well at 12 mo
3	62	M	None	1	60	None	LAD, LCFx, right	3	VF (3 ES)	No VT/VF at EPS	None	Alive and well at 60 mo
4	64	M	Unstable angina	2	47	Anteroseptal	LCFx, right	2	VF (2 ES)	No VT/VF at EPS	None	Alive and well at 24 mo
5	61	M	None	1	45	Anteroseptal, inferobasal	LAD, LCFx, right	3	VF (2 ES)	Spontaneous VF	None	Sudden cardiac death at 6 days
6	69	F	Unstable angina	1	45	Inferior	Right, LCFx	2	VF (2 ES)	No VT/VF at EPS	None	Death due to congestive heart failure at 18 mo
7	63	F	Unstable angina	5	30	Anteroseptal, inferior	LAD, LCFx, right	2[a]	Not done	Spontaneous and inducible VF	Amiodarone	Alive and well at 6 mo
8	62	M	Unstable angina	3	40	Inferior, septal	LAD, right	2	Not done	Spontaneous and inducible VF	Amiodarone	Alive and well at 6 mo

[a] The right coronary artery was too severely diseased to have grafting done.

EPS = electrophysiological study; ES = extrastimuli; LAD = left anterior descending; LCFx = left circumflex; VF = ventricular fibrillation; VT = ventricular tachycardia.

otherwise successful revascularization procedure and that their appearance suggests an ominous prognosis.

Only limited electrophysiological data about the effects of bypass grafting on induced sustained ventricular arrhythmias are available. Morady and associates [19] reported no late deaths or arrhythmia recurrences among 8 patients in whom sudden death was aborted when they were treated by revascularization, but all 8 had had no inducible arrhythmia at a baseline electrophysiological study. Garan and co-workers [20] reported control of inducible ventricular tachycardia or ventricular fibrillation in 10 (59%) of 17 patients. All 4 patients with ventricular fibrillation at initial electrophysiological study had control of their arrhythmia. However, 8 of the remaining 13 patients had only nonsustained ventricular tachycardia preoperatively. Because these authors used only two extrastimuli in their protocol, it is difficult to evaluate whether ventricular fibrillation or ventricular tachycardia was the baseline arrhythmia in these 8 patients.

In this study, we selected only patients with sustained ventricular fibrillation that was shown not to be preceded by monomorphic ventricular tachycardia. In these patients, the response to coronary artery bypass grafting was unpredictable; 5 of the 8 became arrhythmia free but 3 had spontaneous recurrences of ventricular fibrillation despite apparently adequate revascularization. Clinical variables could not be used in this series to select those patients whose arrhythmias were controlled after coronary artery bypass grafting. The presence of preoperative unstable angina did not ensure control, as only 2 of 4 patients with that finding responded. Our series included only 1 patient who did not have akinetic or dyskinetic regions at left ventriculography, and it is possible that patients with normal left ventricular function and ventricular fibrillation may have a higher response rate to coronary bypass procedures. The results of Garan and associates [20] and the CASS study [16] would support this last hypothesis, as the patients in those studies had higher mean left ventricular ejection fractions than did our patients whose mean ejection fraction was only 39%. The mechanism by which inducible arrhythmias respond to revascularization is uncertain, but it is possible that clinically silent resting ischemia is present in some patients during the electrophysiological studies. Such potentially reversible ischemia may contribute to the electrophysiological substrate necessary to induce ventricular fibrillation.

The data presented in this study indicate that coronary artery bypass grafting should not be presumed to provide effective therapy for patients with cardiac arrest and ventricular fibrillation. In a patient resuscitated from cardiac arrest, preoperative studies are necessary to characterize fully the patient's arrhythmia. Even if these studies suggest that the patient is susceptible only to polymorphic arrhythmias, the effects of coronary artery bypass grafting on these arrhythmias are not completely predictable. Appropriate postoperative monitoring and electrophysiological testing are indicated in all such patients. In select patients, implantation of defibrillating leads with later implantation of an automatic implantable cardioverter defibrillator, if postoperative studies are positive, may be the most expeditious surgical approach. In some patients, defibrillator implantation may be preferable to long-term amiodarone therapy with its occasionally toxic side effects.

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REVIEW OF RECENT BOOKS

Atlas of Pulmonary Resections, Second Edition

By Buford H. Burch and Watts R. Webb
Springfield: Charles C. Thomas, 1988
246 pages, illustrated

Reviewed by Richard M. Peters, MD

This is the second edition of the *Atlas of Pulmonary Resections* by Burch and Webb. In my opinion it represents an excellent addition to the atlases of pulmonary resections. Burch and Webb start the book with general discussions of one-lung anesthesia and all of the procedures such as cricothyroidotomy and mediastinoscopy, including a good discussion of the three-stage thoracoplasty which is not so readily available today. They then proceed with a section on technical considerations and procedures during pulmonary resections. The only thoracotomy incision they describe is the classic posterolateral thoracotomy incision with the division of all the muscles. It is regrettable that they have not included more conservative muscle-sparing incisions, which are gaining so much justified popularity at this time. They go into some detail about the techniques of dissection of pulmonary vessels, but have only a very minor discussion of staplers throughout the total presentation. For the uninitiated there are some relatively detailed discussions of techniques of repair of lacerations of the pulmonary arteries and veins. They also provide descriptions of intrapericardial approaches to both pulmonary arteries and all four pulmonary veins. They conclude this with sections on closure of the bronchus using a stapler, with standard end-over sutures, or with breaking up the bow. They have a short discussion on postoperative care at the end of this section, which is disappointing to me in that they bring up none of the newer methods of pain control and concentrate on endotracheal suction rather than on making it easier for the patient to cough.

The final section of the book and the major portion of it is a section on pulmonary resections. This portion of the book is notable because it actually contains drawings and descriptions of segmental resections of the various segments of both lungs. These are both complete and easy to follow. This is, of course, a much needed area and will be very useful to surgeons who are not frequently doing these types of procedures.

The discussions are simple, and in some areas not as complete as this reviewer would like. I would have some differences with them. The description of the anatomy through the mediastinoscope could be clearer. I would differ with Burch and Webb in their bronchial closure with nonabsorbable sutures. We now have good evidence that synthetic absorbable sutures are superior. They also advocate an on the table roentgenogram on all thoracotomy patients to be sure a sponge isn't left in the chest. I believe that is unnecessary and that a brief discussion on careful inspection of the chest cage would be more in order. I also would differ with them on their description of resection of blebs because they resect and remove the blebs, and it is my opinion that it is better to leave the blebs in place because they are less likely to have leaks. These all, of course, are the personal opinions of a different surgeon, but over all this will be a very useful book to residents in training and for a reference book in all cardiothoracic surgeons' libraries.

San Diego, California

Inflammatory Pseudotumor of the Lung in Adults: Radiographic and Clinicopathological Analysis

Teruyoshi Ishida, MD, Takeshi Oka, MD, Toyohiko Nishino, MD,
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Inflammatory pseudotumors of the lung are rare in adults. We treated 7 patients with such tumors and describe the histological evidence, radiographic findings, and surgical treatment. In 5 patients, lung cancer was suspected preoperatively on the basis of the radiographic findings. Intraoperatively, the gross appearance of the pleura resembled lung cancer in 6 patients; the parietal pleura was involved in 3, and pleural indentation was present in the other 3. Two patients underwent partial resection, as the frozen section revealed a benign tumor, and 5 patients underwent lobectomy for what appeared to be lung cancer or a large mass. All of the patients are doing well without other therapy. We believe the lesion should be differentiated from lung cancer at operation by frozen sections, even though this proved pertinent in only 2 of the 7 patients. Limited resection is recommended if the lesion is an inflammatory pseudotumor.

(Ann Thorac Surg 1989;48:90–5)

Inflammatory pseudotumors of the lung are uncommon in the thoracic surgical literature. These lesions, which show a close radiographic resemblance to carcinoma of the lung [1], are nonneoplastic pulmonary masses of unknown etiology and are composed of a variety of inflammatory and mesenchymal cells, including plasma cells, histiocytes, lymphocytes, and spindle-shaped mesenchymal cells [2]. These masses have been called plasma cell granuloma, postinflammatory pseudotumor, fibrous histiocytoma, fibroxanthogranuloma, and solitary mast cell granuloma [3]. The most commonly used names include inflammatory pseudotumor and plasma cell granuloma.

We describe here the radiographic and histological characteristics of this lesion in 7 adults treated surgically for inflammatory pseudotumor of the lung.

Material and Methods

Seven patients with inflammatory pseudotumor of the lung were treated in the Second Department of Surgery, Faculty of Medicine, Kyushu University, between 1974 and 1987. Age, sex, history of smoking, and history of lung infections were recorded. Routine physical examination, chest roentgenography, computed tomography of the thorax, sputum cytology, bronchoscopy, hematology, and blood chemical analysis were done. The resected specimens were fixed in 10% formalin, paraffin sections were prepared, and the sections were stained with hematoxylin and eosin.

Results

Clinical Features

The patients included 5 men and 2 women aged 28 to 73 years (average age, 53 years). Five were asymptomatic, and 2 showed the usual symptoms related to lung disease, including cough, sputum, and hemoptysis. There were 5 smokers, and the cigarette index of Geoffrey and associates [4] ranged from 160 to 1,050.

Physical examination on admission was unremarkable. For all patients, the results of sputum cytology and bronchoscopy were negative for malignant cells. The laboratory data, including hematology, urinalysis, and blood chemistry, were within normal limits in most instances.

Radiographic Findings

The solitary mass was located in the right upper lobe in 3 patients, the right lower lobe in 1 patient, the left upper lobe in 2, and the left lower lobe in 1 (Table 1). The edge of the mass was ill defined in 5 and well circumscribed in 2. Among the 5 patients with ill-defined margins, 2 had spicular radiation resembling carcinoma (Fig 1A). Four patients had pleural indentation (Fig 1B), and 4 had cavitation (Fig 1C), with vascular convergence in 1. The two well-circumscribed masses showed round shadows with smooth borders (Fig. 1D). Computed tomography demonstrated the ill-defined solitary mass with spicular radiation resembling carcinoma in 5 patients (Fig 2A). The other 2 patients had a round solitary mass (Fig 2B), with irregular cavities in one mass (Fig 2C). Lung cancer was suspected preoperatively in 5 patients as a result of the radiographic examinations.

Accepted for publication Feb 14, 1989.

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Table 1. Radiographic Evidence of Inflammatory Pseudotumor of Lung

Patient No.	Location	Solitary Mass	Spicular Radiation	Pleural Indentation	Cavitation	Vascular Convergence
1	RLL	Present	Absent	Present	Absent	Absent
2	LUL	Present[a]	Absent	Absent	Absent	Absent
3	RUL	Present	Present	Present	Present	Absent
4	RUL	Present	Absent	Present	Present	Present
5	RUL	Present[a]	Absent	Absent	Present	Absent
6	LUL	Present	Present	Present	Absent	Absent
7	LLL	Present	Absent	Absent	Present	Absent

[a] This was one of two well-circumscribed lesions.

LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RUL = right upper lobe.

Operative and Pathological Findings

The diameter of the tumors ranged from 8 to 60 mm (mean diameter, 30 mm) (Table 2). Of the seven tumors, six were peripherally located and 1, centrally located. The pleural changes resembled those of lung cancer. Three tumors partially involved the parietal pleura, and the others were covered with pleural indentation. Two patients underwent partial resection of the lung, and the

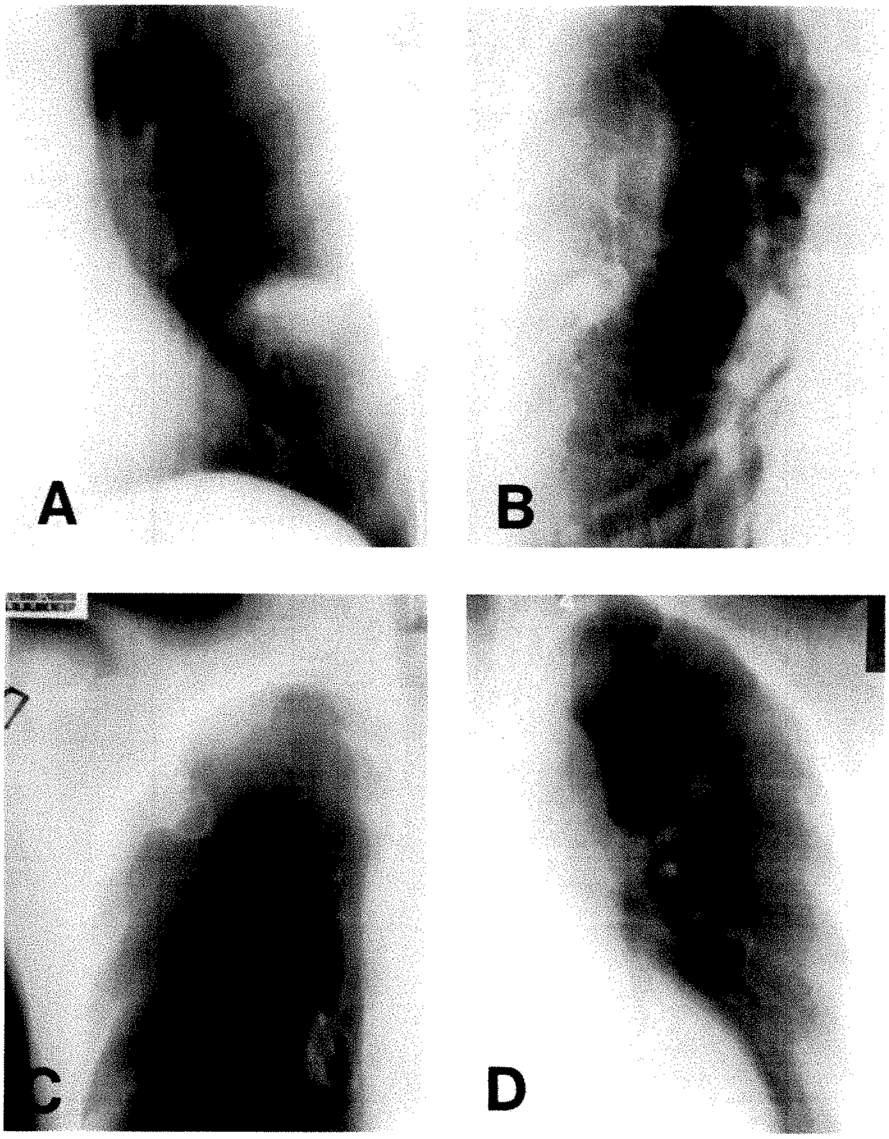

Fig 1. (A) (Patient 6.) Tomogram of the left chest shows a solitary nodular lesion with ill-defined margins. Note spicular radiation, which resembles that in lung cancer. (B) (Patient 3.) Tomogram of the right chest shows a nodular lesion with ill-defined margins. Note pleural indentation and spicular radiation, which are found in lung cancer. (C) (Patient 5.) Tomogram of the right chest shows a well-circumscribed lesion with irregular cavities. (D) (Patient 2.) Tomogram of the left chest shows a well-circumscribed round lesion, which appeared benign.

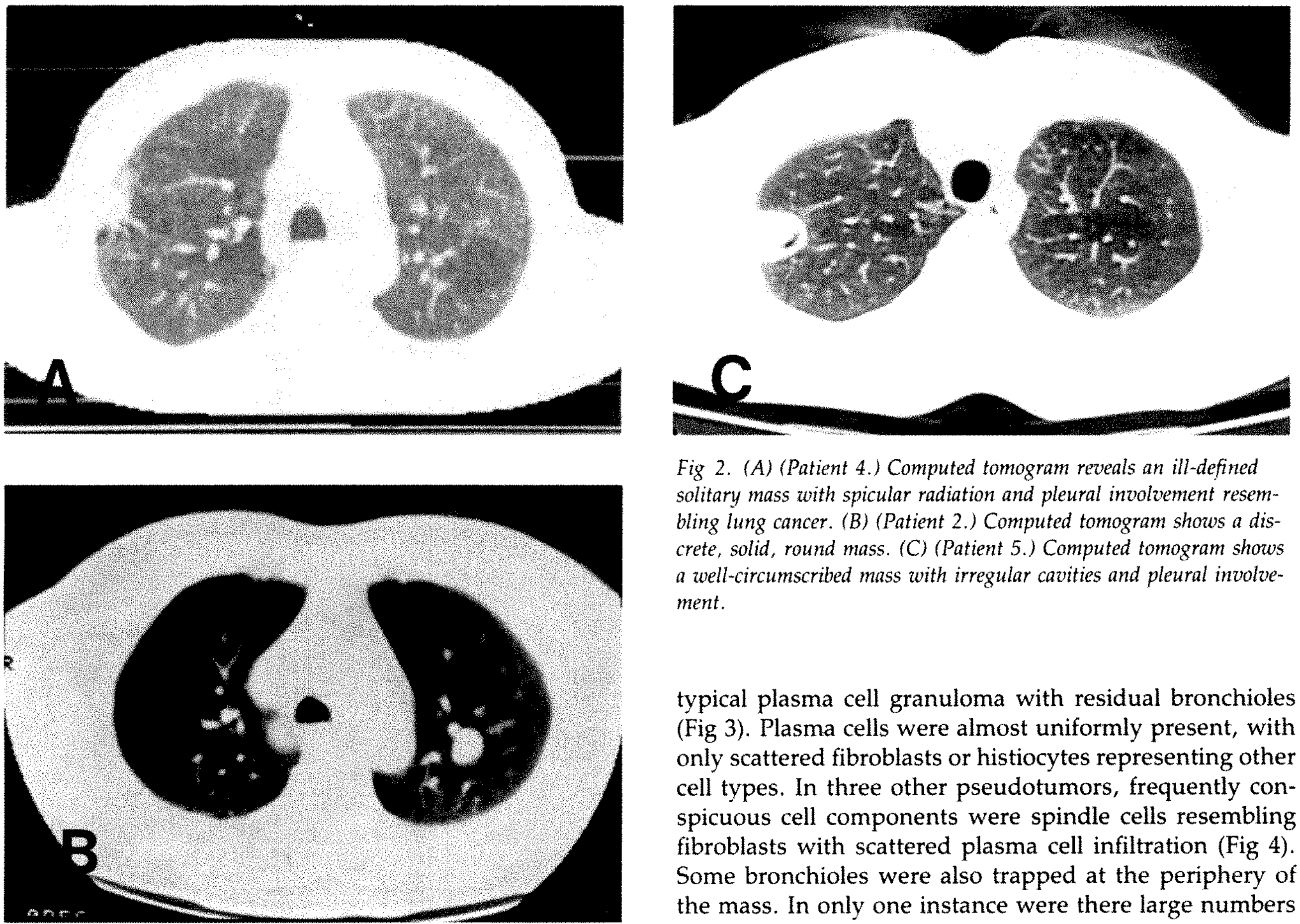

Fig 2. (A) (Patient 4.) Computed tomogram reveals an ill-defined solitary mass with spicular radiation and pleural involvement resembling lung cancer. (B) (Patient 2.) Computed tomogram shows a discrete, solid, round mass. (C) (Patient 5.) Computed tomogram shows a well-circumscribed mass with irregular cavities and pleural involvement.

frozen section done intraoperatively revealed a "benign" tumor. The other 5 patients underwent lobectomy. Frozen section was not done because of the resemblance to lung cancer or large mass.

Gross examination revealed a circumscribed mass and necrotic cavities in four of the masses. Microscopically, there was the absence of a true capsule and interstitial spread into the adjacent lung parenchyma, with trapping and preservation of small air spaces in the mass.

Three different cell types were seen: plasma cells, spindle cell–like fibroblasts, and xanthomatous histiocytes. Three of the inflammatory pseudotumors showed a typical plasma cell granuloma with residual bronchioles (Fig 3). Plasma cells were almost uniformly present, with only scattered fibroblasts or histiocytes representing other cell types. In three other pseudotumors, frequently conspicuous cell components were spindle cells resembling fibroblasts with scattered plasma cell infiltration (Fig 4). Some bronchioles were also trapped at the periphery of the mass. In only one instance were there large numbers of xanthomatous histiocytes with infiltration of varying numbers of plasma cells and lymphocytes (Fig 5).

Follow-up

Follow-up ranges from 1 to 5 years. All patients are doing well, and there is no evidence of recurrence.

Comment

Inflammatory pseudotumor of the lung is a well-characterized clinical entity and on chest roentgenograms and computed tomograms resembles a tumor. Several terms have been used for this lesion, and it does not have a precise pathological classification [3]. The incidence of

Table 2. Intraoperative Findings in Patients With Inflammatory Pseudotumor of Lung

Patient No.	Location	Size (mm)	Pleura Involved Macroscopically	Frozen Section at Operation	Operation	Predominant Cell Type
1	RLL (S6)	8 × 8	Indentation	No	Lobectomy	Spindle cell
2	LUL (S1 + 2)	19 × 15	(Central area)	No	Lobectomy	Spindle cell
3	RUL (S3)	20 × 10	Indentation	Yes	Partial lung resection	Plasma cell
4	RUL (S3)	20 × 20	Parietal pleura	Yes	Partial lung resection	Spindle cell
5	RUL (S2)	30 × 30	Parietal pleura	No	Lobectomy	Xanthomatous histiocyte
6	LUL (S5)	60 × 60	Indentation	No	Lobectomy	Plasma cell
7	LLL (S10)	55 × 55	Parietal pleura	No	Lobectomy	Plasma cell

LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RUL = right upper lobe; S = segment.

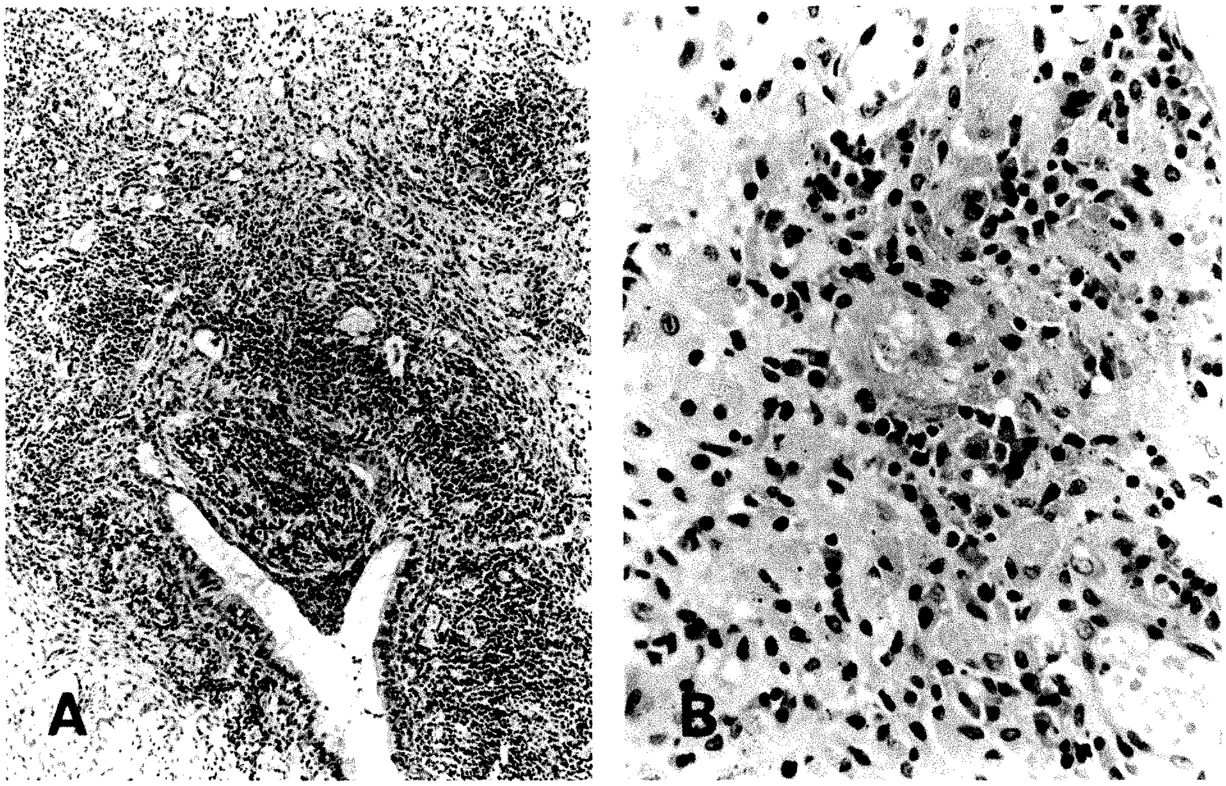

Fig 3. (Patient 6.) Photomicrographs show an inflammatory pseudotumor. (A) The mass has trapped bronchioles and has spread interstitially. (B) Plasma cell infiltration is predominant, but other inflammatory cells and mesenchymal spindle cells are present. (Both, hematoxylin and eosin; A, ×80, B, ×320 before 10% enlargement.)

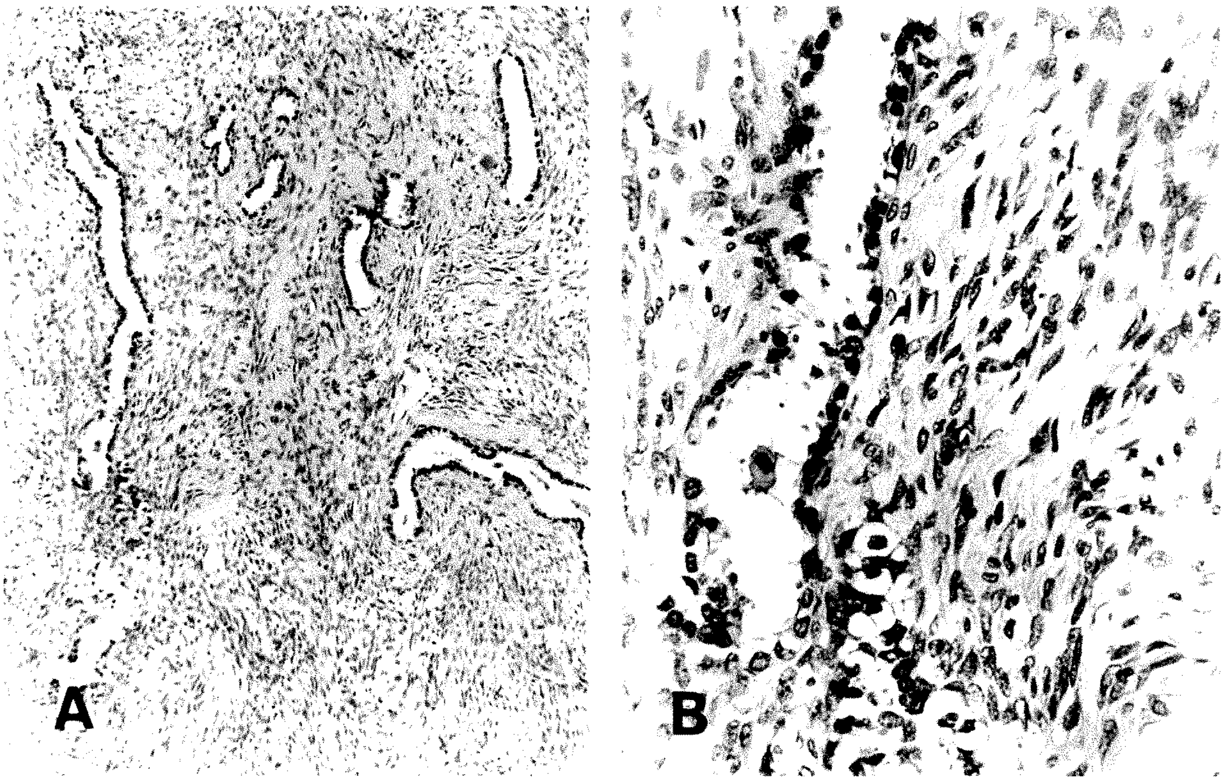

Fig 4. (Patient 2.) Photomicrographs show an inflammatory pseudotumor. (A) This lesion is composed predominantly of mesenchymal spindle cells, and there is trapping and preservation of air spaces. (B) The mesenchymal spindle cells are prominent, and there are a few plasma cells. (Both, hematoxylin and eosin; A, ×80, B, ×320 before 10% enlargement.)

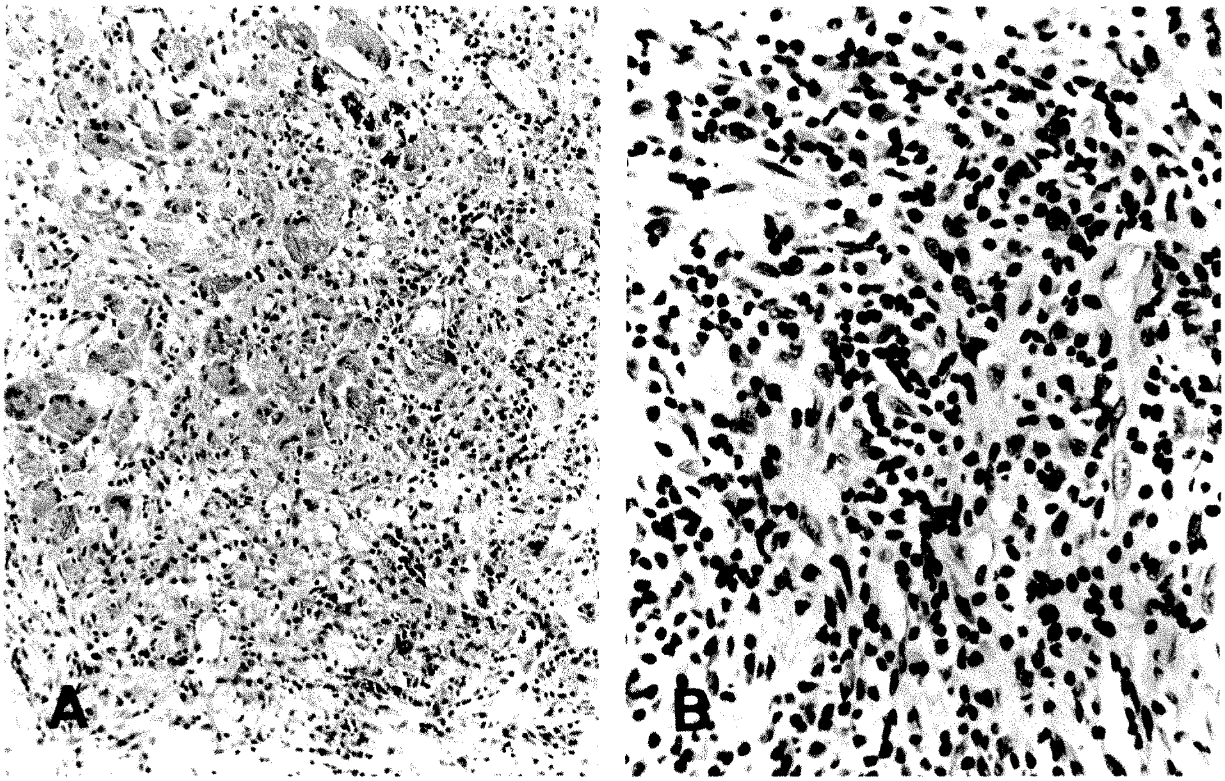

Fig 5. (Patient 5.) Photomicrographs reveal an inflammatory pseudotumor with a predominant pattern of xanthomatous histiocytes. Large xanthomatous histiocytes are present among the plasma cell infiltrations. (Both, hematoxylin and eosin; A, ×126, B, ×320 before 10% enlargement.)

inflammatory pseudotumor of the lung is reported to be 0.7% of all pulmonary tumors [5]. These tumors most often occur in children less than 16 years of age [6]. Among 718 pulmonary tumors diagnosed in our department of surgery between 1974 and 1987, seven (1.0%) were inflammatory pseudotumors of the lung.

Inflammatory pseudotumor of the lung is relatively difficult to diagnose [7]. In radiographic studies, there are no specific signs suggestive of the disease [8]. A well-circumscribed lesion is considered to be benign and a lesion with ill-defined margins, malignant. We noted lesions with spicular radiation, pleural indentation, vascular convergence, or a combination of these, findings closely resembling those in patients with lung cancer. Laboratory findings do not aid in establishing the diagnosis of inflammatory pseudotumor [2]. Sputum and bronchoscopic studies also yield no evidence of organisms or malignant cells [7]. Repeat percutaneous needle biopsy has been recommended as a feasible approach to use in diagnosing inflammatory pseudotumor [9], but this method does not always rule out malignancy [10]. Only resection leads to an accurate diagnosis of these lesions. If the tumor is malignant, metastasis will occur; hence, the lesions are treated surgically.

In some lesions, the intraoperative gross appearance resembles that of lung cancer with pleural indentation or parietal pleural involvement. If an inflammatory pseudotumor is suspected at operation, partial resection and frozen section is recommended [11]. When the lesion is benign, a limited resection is indicated. When a limited resection is difficult or the diagnosis of malignancy cannot be excluded, lobectomy is done [2].

The etiology of this lesion is unclear. Infection or inflammatory agents have been identified [2]. Other suspected causes include viral infection, immunological reaction, and disorders of cholesterol metabolism [7]. However, inflammatory pseudotumor of the lung has been regarded as a variant of an inflammatory repair process rather than a true neoplastic process [12]. Immunohistochemically, the plasma cells infiltrating this lesion show polyclonality [13, 14].

We emphasize the difficulty of establishing preoperatively the diagnosis of inflammatory pseudotumor of the lung. This lesion must be kept in mind when adults are seen with radiographic findings suggestive of lung cancer, especially when sputum cytology and bronchoscopic biopsy are negative for malignant cells. If the lesion seems to be an inflammatory pseudotumor, we recommend a limited pulmonary resection.

We thank M. Ohara for critical comments.

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The Effect of Fluorocarbon Emulsion on 24-Hour Canine Heart Preservation by Coronary Perfusion

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This study was designed to evaluate the effects of fluorocarbon emulsion as an oxygen carrier in myocardial preservation. The hearts were preserved for 24 hours by coronary perfusion with either oxygenated crystalloid cardioplegic solution (group C) or crystalloid cardioplegic solution with fluorocarbon added (group FC). The perfusion pressure was kept at 20 mm Hg, and myocardial temperature was maintained at 4°C. Group FC demonstrated better recovery in developed pressure and maximum rate of rise of left ventricular pressure compared with group C. The postpreservation end-diastolic pressure in group C increased significantly compared with the baseline value (value obtained before preservation). On the other hand, group FC showed no significant increase of end-diastolic pressure after preservation. Group FC released a significantly lower level of creatine kinase into its perfusate than did group C. Ultrastructural changes after preservation in group C showed severe ischemic injury, but there was no evidence of ischemic injury in group FC. The use of fluorocarbon emulsion proved beneficial to myocardial protection in long-term preservation of canine hearts.

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The operative techniques involved in heart transplantation have progressed substantially since Hardy and associates [1] reported clinical heart transplantation in 1964. However, long-term heart preservation is one of the major limiting factors in heart transplantation. There are two methods of heart preservation. One is coronary perfusion, and the other is simple immersion. It has been suggested that coronary perfusion is superior to simple immersion for long-term preservation. Many methods of coronary perfusion have been reported. Myocardial cooling and oxygenation of the perfusate reduce anaerobic metabolism and maintain energy stores during ischemia, respectively. This study was designed to evaluate the effect of fluorocarbon emulsion [2] as an oxygen carrier in myocardial preservation.

Material and Methods

Thirteen dogs weighing 10 to 15 kg were anesthetized with thiamylal sodium (10 to 20 mg/kg) and maintained on a volume-controlled respirator with room air. The right femoral artery and femoral vein were cannulated for blood sampling and for fluid infusion, respectively. The heart was exposed through a thoracotomy in the right fourth intercostal space. The azygos vein was ligated and divided. After systemic heparinization (3 mg/kg), 200 mL of blood was removed through the catheter in the femoral artery. A large needle was inserted into the root of the aorta for the infusion of cardioplegic solution. After the ascending aorta was clamped, 100 mL of cold (4°C) crystalloid cardioplegic solution was infused, and ice slush was poured over the heart. At the same time, the superior and inferior venae cavae were ligated and the right atrial appendage was incised.

The heart was excised immediately after cardiac arrest and immersed in cardioplegic solution (4°C). A cannula was inserted into the aortic stump for perfusion, and a latex balloon was positioned in the left ventricle through the mitral annulus to measure intracavitary pressure. The isolated heart was suspended in a perfusion circuit primed with autogenous blood and Ringer's lactate.

Baseline measurements of isovolemic left ventricular function were taken during right ventricular pacing at 120 beats per minute. The perfusion pressure was kept at 80 mm Hg. After the baseline measurements had been completed, 100 mL of cardioplegic solution was infused to

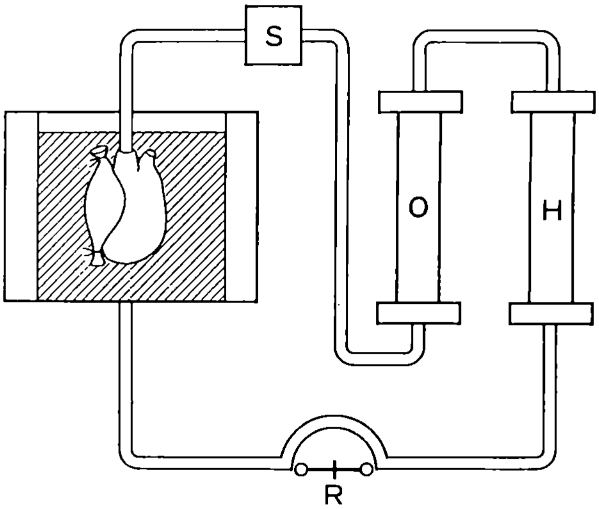

Fig 1. Preservation apparatus. (H = *heat exchanger;* O = *oxygenator;* R = *roller pump;* S = *sensor of pressure, pH, and temperature.)*

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Table 1. Composition of Perfusates

Variable	Group C	Group FC
Na (mEq/L)	25.2	76.4
K (mEq/L)	23.0	23.0
Ca (mEq/L)	1.3	1.3
Mg (mEq/L)	5.0	3.1
Cl (mEq/L)	26.6	69.2
Glucose (g/L)	50.0	25.9
pH	7.98 (4°C)	8.00 (4°C)
Osmolarity (mosm/L)	380–400	330–350
Oncotic pressure (mm H_2O)	. . .	380–395
Soluble oxygen (mL/L)	14.3 ± 4.9	44.5 ± 6.1

induce cardiac arrest. After this, the heart was transferred to the preservation apparatus (ORPH 2000 C; Senkoh Medical Instruments, Tokyo, Japan) (Fig 1).

The heart was preserved for 24 hours by coronary perfusion with either oxygenated crystalloid cardioplegic solution (group C; n = 6) or crystalloid cardioplegic solution with fluorocarbon added (group FC; n = 7). The composition of the two perfusates is shown in Table 1. The perfusate used in group FC was formulated by mixing equal parts of fluorocarbon (FC-43 Emulsion) (The Green Cross Corp, Tokyo, Japan) and group C perfusate. Then potassium chloride was added to give a concentration of 23 mEq/L of potassium. The perfusion pressure was kept at 20 mm Hg, the myocardial temperature was maintained at 4°C, and the perfusate pH was kept at 8.0. The volume of perfusate used was 1 L, and this was recirculated. When the perfusate pH decreased, it was regulated with bicarbonate.

After 24-hour preservation, the heart was removed from the preservation apparatus and reperfused with normothermic blood on the perfusion circuit for 60 minutes. Postpreservation left ventricular function was measured at 60 minutes under the same conditions as the baseline measurement. A biopsy sample was taken from the left ventricular apex before and after reperfusion to measure myocardial water content and evaluate ultrastructural change. The total creatine kinase (CK) level of the perfusate after preservation was measured.

Isovolemic Left Ventricular Function

The left ventricular intraballoon pressures and maximum rate of rise of left ventricular pressure were measured at 5-mL increments of balloon volume (from 5 to 20 mL) using a four-channel polygraph (amplifier Case 7746; San-ei Corp, Tokyo, Japan) and recorded with a pen oscillograph (8 Kll; San-ei Corp). For each balloon volume, the ratios of the postpreservation and baseline values (percent recovery) of left ventricular developed pressure and maximum rate of rise of left ventricular pressure were calculated. Equations for the slope of the end-systolic pressure–volume relation, E max, representing contractility, and the slope of the volume–end-diastolic pressure relation, distensibility, representing compliance, were constructed.

Myocardial Water Content

Samples were desiccated for 48 hours at 60°C. Then the water content was calculated using the following equation:

$$\text{Myocardial water content (\%)} = (1 - [\text{dry weight/wet weight}]) \times 100.$$

Coronary Resistance

Perfusion pressure was maintained at 80 mm Hg by adjusting the rotation frequency of the roller pump. Coronary flow was calculated from the flow volume per rotation and the frequency of revolution in the perfusion circuit. Coronary resistance was calculated using the following equation:

$$\text{Coronary resistance (mm Hg/mL/s)} = 80/\text{coronary flow}.$$

Total Creatine Kinase Release

The amount of CK released into the perfusate during 24-hour preservation per 100 g of left ventricle was measured to determine the extent of myocardial injury. Creatine kinase was measured by the UV method.

Table 2. Left Ventricular Function at Baseline (Before Preservation)[a,b]

	Balloon Volume (mL)							
	Group C				Group FC			
Variable	5	10	15	20	5	10	15	20
Developed pressure (mm Hg)	40.7 ± 7.1	61.5 ± 11.4	79.0 ± 11.6	93.3 ± 13.1	38.1 ± 4.2	65.1 ± 9.7	88.0 ± 14.1	102.4 ± 13.7
dP/dt_{max} (mm Hg/s)	633 ± 84.5	950 ± 204.5	1267 ± 233.5	1483 ± 244.1	750 ± 99.2	993 ± 153.6	1293 ± 212.5	1464 ± 252.9
LVEDP (mm Hg)	0.7 ± 0.7	4.3 ± 1.5	10.2 ± 3.5	15.0 ± 4.0	0.4 ± 0.4	3.4 ± 0.9	7.4 ± 1.4	11.1 ± 1.8
E max (mm Hg/mL)[c]	4.47 ± 0.95				5.36 ± 0.81			
Distensibility (mL/mm Hg)[c]	1.85 ± 0.40				1.69 ± 0.38			

[a] Data are shown as the mean ± the standard error of the mean. [b] No significant differences were found in baseline measurements of left ventricular function between group C and group FC. [c] Balloon volumes were not applicable for these measurements.

dP/dt_{max} = maximum rate of rise of left ventricular pressure; E max = contractility; LVEDP = left ventricular end-diastolic pressure.

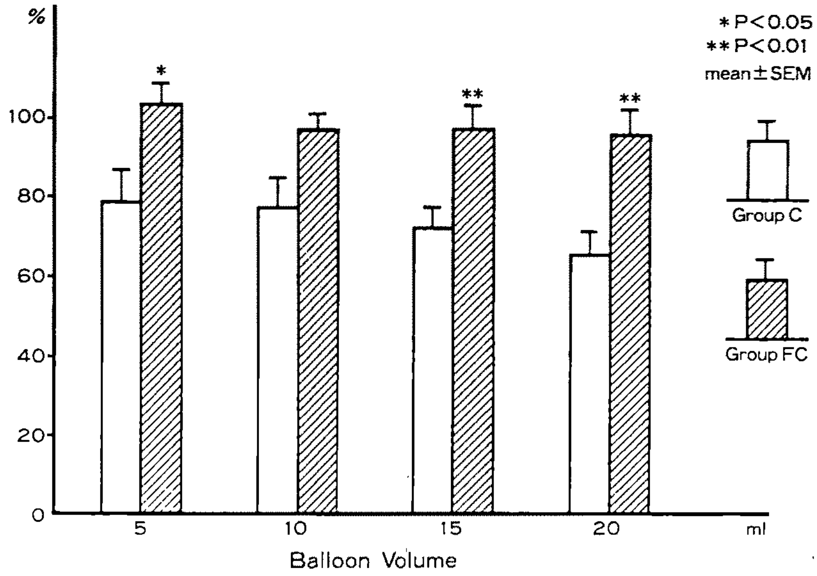

Fig 2. Percent recovery of developed pressure. Group FC demonstrated better recovery than group C at balloon volumes of 5 mL (p < 0.05), 15 mL (p < 0.01), and 20 mL (p < 0.01). (SEM = standard error of the mean.)

Ultrastructural Appearance

Transmural specimens were fixed in 2.5% glutaraldehyde in 0.1 mol/L of cacodylate buffer, postfixed in 1% osmium tetroxide, and embedded in Epon-araldite. Ultrathin sections were made and stained with uranyl acetate and lead citrate for electron microscopic examination (JEM-2000 CX; Nippon Denshi Corp, Tokyo, Japan).

A comparison of ultrastructural changes in the hearts of group C versus the hearts of group FC was conducted by evaluating the density of glycogen granules, interstitial edema, and mitochondria. Mitochondrial scores were calculated by the method of Hashiba [3]. For each heart, five electron micrographs of the midmyocardial layer were taken. In each micrograph, five mitochondria were graded with a score of 0 through 4, as described by Jennings and Ganote [4]. Therefore, a total of 25 mitochondria were evaluated, and the mitochondrial score ranged from 0 through 100.

Data Analysis

Statistical analysis was performed using Student's *t* test. The values were expressed as the mean ± the standard error of the mean. Two values were considered significantly different if the *p* value was less than 0.05.

Results

No significant differences were found between group C and group FC for baseline left ventricular function (Table 2).

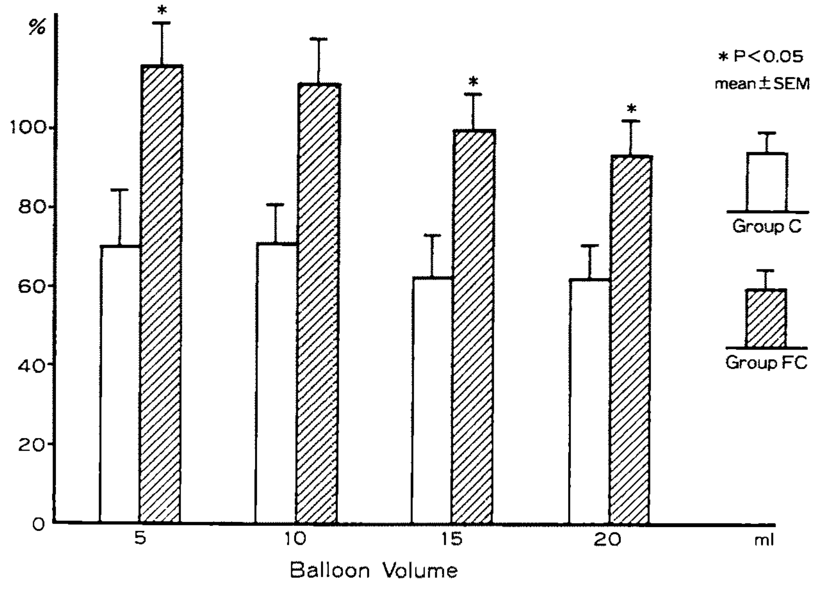

Fig 3. Percent recovery of maximum rate of rise of left ventricular pressure. Group FC demonstrated better recovery at balloon volumes of 5 mL, 15 mL, and 20 mL (p < 0.05). (SEM = standard error of the mean.)

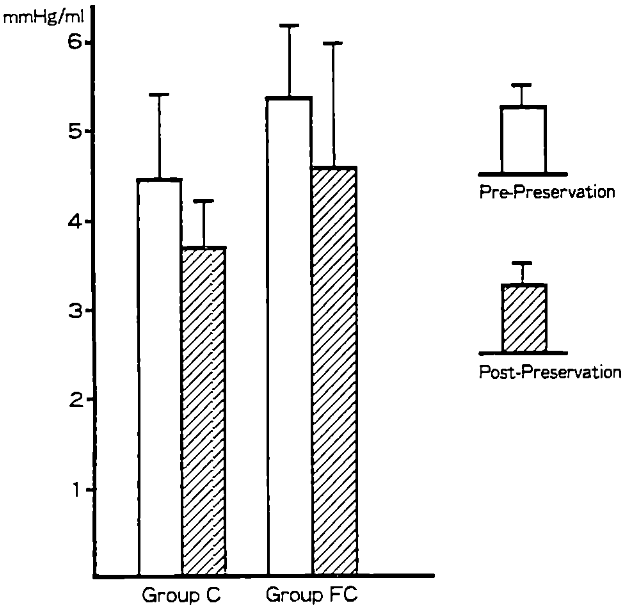

Fig 4. End-systolic pressure–volume relationship or E max. Neither group showed a significant decrease in the value obtained after preservation compared with the baseline value. Values are shown as the mean ± the standard error of the mean.

Isovolemic Left Ventricular Function

The percent recovery of left ventricular developed pressure after preservation in group C was 78.7% ± 8.2% at a balloon volume of 5 mL, 77.5% ± 7.8% at 10 mL, 72.5% ± 5.1% at 15 mL, and 67.5% ± 5.9% at 20 mL. The values in group FC were 103.4% ± 5.2% at 5 mL, 97.0% ± 4.0% at 10 mL, 97.4% ± 6.0% at 15 mL, and 96.0% ± 6.6% at 20 mL. Group FC demonstrated significantly better recovery of developed pressure than group C at balloon volumes of 5, 15, and 20 mL ($p < 0.05$, $p < 0.01$, and $p < 0.01$, respectively) (Fig 2).

The percent recovery of maximum rate of rise of left ventricular pressure after preservation in group C was 70.5% ± 13.7% at a balloon volume of 5 mL, 71.0% ± 17.2% at 10 mL, 62.3% ± 11.3% at 15 mL, and 62.5% ± 9.5% at 20 mL. The values in group FC were 115.7% ± 12.8% at 5 mL, 111.6% ± 11.8% at 10 mL, 100.1% ± 9.3% at 15 mL, and 94.0% ± 8.9% at 20 mL. Group FC demonstrated significantly better recovery of maximum rate of rise of left ventricular pressure than group C at balloon volumes of 5, 15, and 20 mL ($p < 0.05$) (Fig 3).

In both groups, postpreservation E_{max} showed no significant decrease compared with the baseline value (Fig 4).

Postpreservation left ventricular end-diastolic pressure in group C increased significantly compared with the baseline value at balloon volumes of 15 and 20 mL ($p < 0.05$). This indicates a decrease in the compliance of the left ventricle after preservation. In contrast, group FC showed no significant increase in postpreservation end-diastolic pressure, and the compliance of the left ventricle was almost unchanged after preservation (Fig 5).

In group C, postpreservation left ventricular distensibility (0.58 ± 0.08 mL/mm Hg) decreased significantly compared with the baseline value (1.85 ± 0.40 mL/mm Hg) ($p < 0.05$). In group FC, the baseline value was 1.69 ± 0.28 mL/mm Hg and the postpreservation value, 1.41 ± 0.22 mL/mm Hg; there was no significant decrease in left ventricular distensibility after preservation (Fig 6).

Myocardial Water Content

The values for myocardial water content at baseline and after reperfusion were 80.0% ± 1.1% and 83.7% ± 1.0% in group C and 74.3% ± 1.2% and 79.1% ± 0.6% in group FC, respectively. In both groups, postreperfusion myo-

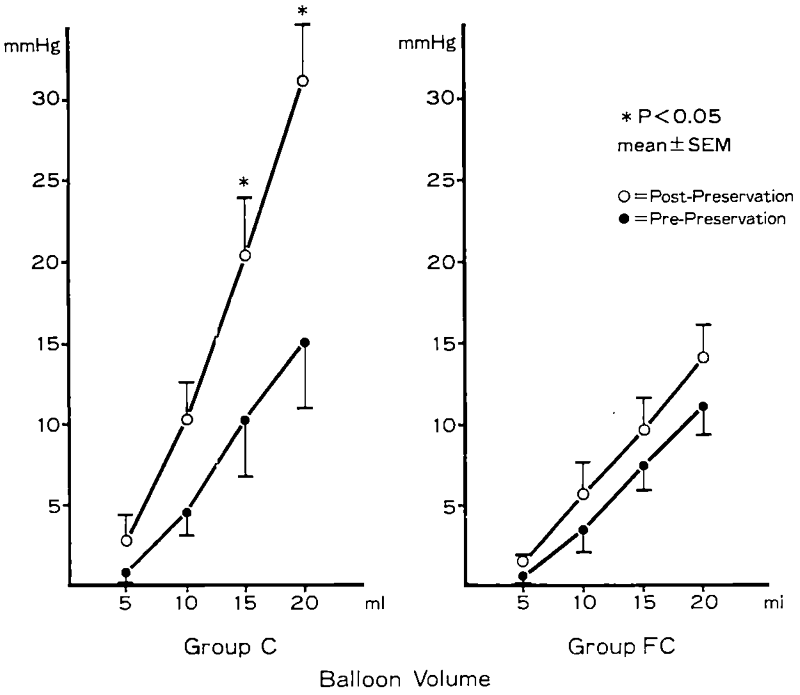

Fig 5. Relationship between left ventricular end-diastolic pressure and balloon volume. The end-diastolic pressure after preservation in group C increased significantly compared with the baseline value at balloon volumes of 15 and 20 mL ($p < 0.05$). On the other hand, group FC showed no significant increase. (SEM = standard error of the mean.)

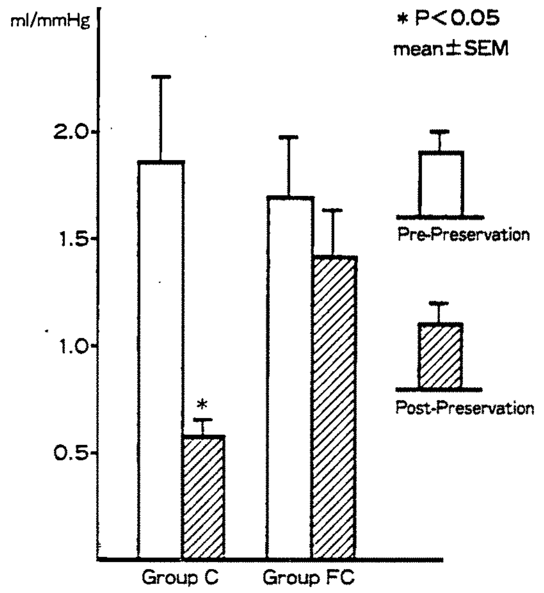

Fig 6. Distensibility. In group C, distensibility decreased significantly after preservation compared with baseline (p < 0.05). Group FC, on the other hand, showed no significant decrease. (SEM = standard error of the mean.)

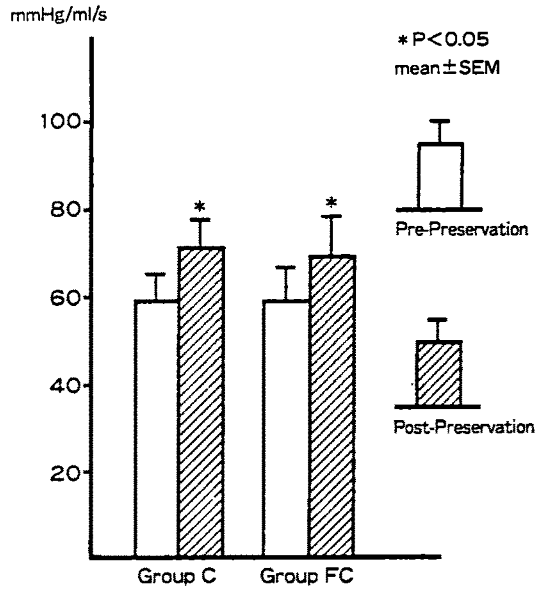

Fig 8. Coronary resistance. There was a significant increase in coronary resistance after preservation in both groups compared with baseline (p < 0.05). (SEM = standard error of the mean.)

cardial water content increased significantly compared with the baseline value, but for both values, group FC showed significantly lower water content than group C ($p < 0.01$) (Fig 7).

Coronary Resistance

The values for coronary resistance at baseline and after preservation were 59.3 ± 13 mm Hg/mL/s and 71.1 ± 16 mm Hg/mL/s in group C and 59.5 ± 22 mm Hg/mL/s and 68.3 ± 25 mm Hg/mL/s in group FC, respectively. The postpreservation coronary resistance was significantly higher than the baseline value in both groups ($p < 0.05$), but there was no significant difference in coronary resistance between group C and group FC (Fig 8).

Total Creatine Kinase Release

The amount of CK released into the perfusate was 407.2 ± 27.8 IU/100 g of left ventricle in group C and 75.4 ± 14.2

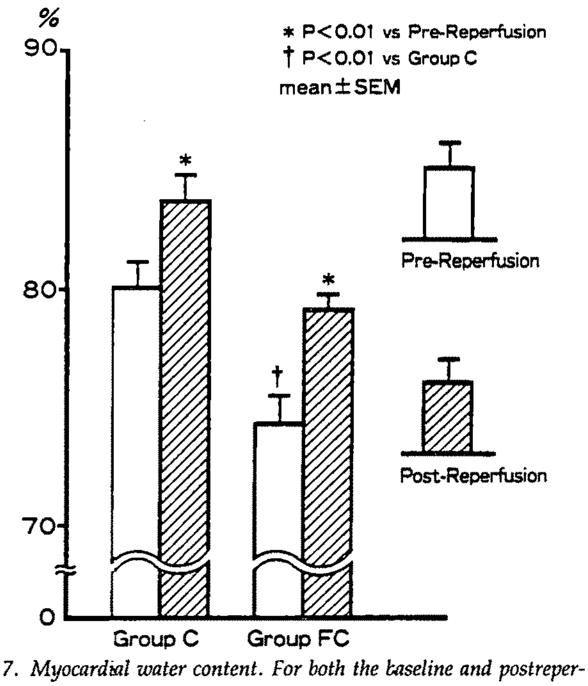

Fig 7. Myocardial water content. For both the baseline and postreperfusion values, group FC showed significantly lower water content than group C (p < 0.01). (SEM = standard error of the mean.)

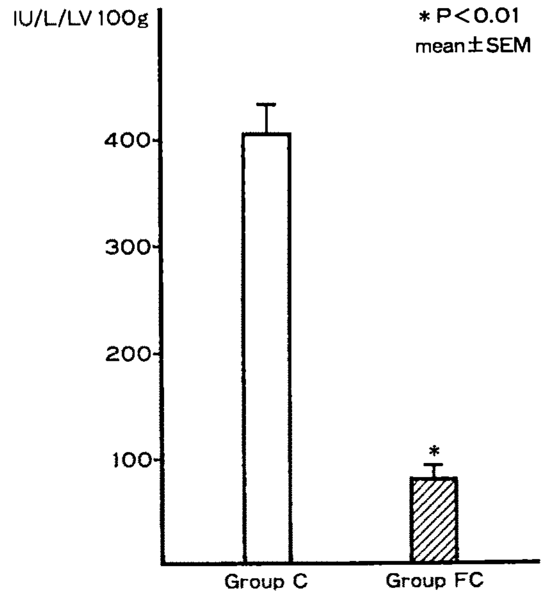

Fig 9. Total creatine kinase release. Group FC released a significantly lower level of creatine kinase into its perfusate than did group C (p < 0.01). (SEM = standard error of the mean.)

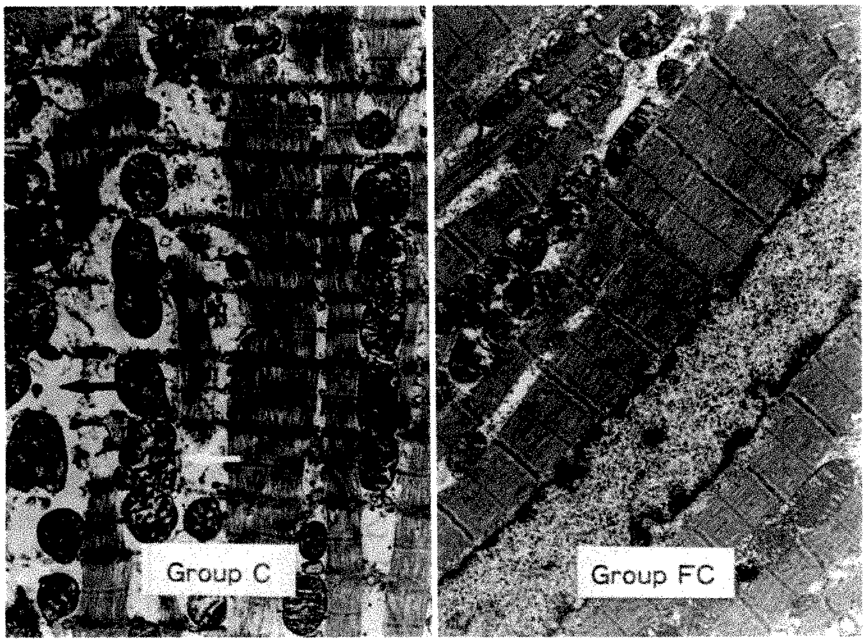

Fig 10. Ultrastructural appearance. In group C, severe ischemic injury was indicated by marked mitochondrial swelling (white arrow), *cristal disruption, marked intracellular edema* (black arrow), *and myofibrillar damage. Group FC showed no evidence of ischemic injury. (Uranyl acetate and lead citrate;* ×*5,000.)*

IU/L/100 g of left ventricle in group FC. Group FC released a significantly lower level of CK into its perfusate than group C ($p < 0.01$) (Fig 9).

Ultrastructural Appearance

Severe ischemic injury in group C hearts after reperfusion was indicated by marked mitochondrial swelling, cristal disruption, marked intracellular edema, and myofibrillar damage. There was no evidence of ischemic injury in hearts from group FC after reperfusion (Fig 10). In group FC, the density of glycogen granules was high and interstitial edema was slight compared with the findings in group C. In group C, the postreperfusion mitochondrial score was significantly lower than the baseline score. In contrast, group FC did not demonstrate a significant change in the mitochondrial score after reperfusion (Table 3).

Comment

The reduction of myocardial energy requirements, the supply of oxygen and substrate to meet basal aerobic metabolic demands, and the washout of metabolic products are considered essential for the long-term preservation of an excised graft. For this reason, hypothermic continuous-perfusion preservation, as reported by Proctor and Parker [5], is superior to simple immersion. Since this system was introduced, various improvements in perfusates and perfusion methods have been reported [6].

Table 3. Ultrastructural Changes[a]

	Group C		Group FC	
Variable	Before Reperfusion	After Reperfusion	Before Reperfusion	After Reperfusion
Density of glycogen granules				
High	1	0	4	3
Moderate	3	1	3	4
Low	2	5	0	0
Interstitial edema				
Slight	3	0	7	6
Moderate	3	6	0	1
Severe	0	0	0	0
Mitochondrial score[b]	76.5 ± 4.4	58.3 ± 6.6[c]	81.0 ± 5.2	76.7 ± 8.7[d]

[a] The integers represent the number of hearts affected and the extent of the change. In group FC, density of glycogen granules was high and interstitial edema was slight compared with group C. In group C, mitochondrial score after reperfusion was significantly lower than the baseline score. In group FC, there was no significant change in the score after reperfusion. [b] Data are shown as the mean ± the standard deviation. [c] Significance: $p < 0.01$ versus baseline. [d] Significance: $p < 0.01$ versus group C.

Oxygen Supply

It has been clearly shown that blood cardioplegia supplying oxygen and substrate markedly enhances myocardial protection in clinical open heart operations. Buckberg [7] showed that blood cardioplegia is effective with respect to delivery of oxygen, production of adenosine triphosphate (ATP), maintenance of oncotic pressure, and buffer capacity. It is well known that hypothermia lowers energy requirements. However, the adverse effects of hypothermia are possible sludging and aggregation of red blood cells and increased viscosity, which may impair subsequent capillary perfusion. Also, the shift to the left of the oxygen-hemoglobin dissociation curve caused by hypothermia diminishes oxygen supply capability. Daggett and associates [8] compared oxygenated blood cardioplegia and oxygenated crystalloid cardioplegia for myocardial protection. They demonstrated that blood cardioplegia is superior to crystalloid cardioplegia at a myocardial temperature of 20°C but not 10°C.

In contrast, FC-43 Emulsion is a perfluorocarbon solution characterized by high oxygen solubility and high oxygen delivery over a wide temperature range. FC-43 Emulsion is much smaller in diameter than a red blood cell, and the oxygen dissociation curve for perfluorocarbon is linear rather than sigmoid, whereas the same temperature reduction leads to increased oxygen delivery with perfluorocarbon. Kanter and associates [2] compared perfluorocarbon cardioplegia, crystalloid cardioplegia, and blood cardioplegia. They reported that perfluorocarbon cardioplegia was superior to the other two, and they also found that the oxygen tension of the myocardium and the oxygen consumption at 17°C with blood and crystalloid cardioplegia were not significantly different. Rousou and associates [9] reported good preservation of ATP using perfluorocarbon cardioplegia.

In this study, the oxygen tension of the perfusate was 259.6 ± 88.7 mm Hg for group C and 412.3 ± 56.3 mm Hg for group FC, and dissolved oxygen was 14.3 ± 4.9 mL of O_2/L for group C and 44.5 ± 6.1 mL of O_2/L for group FC. Bodenhamer and associates [10] calculated oxygen delivered and consumed by measuring the oxygen content of the afferent and efferent cardioplegic solution in their comparative study of oxygenated versus nonoxygenated crystalloid cardioplegia. They demonstrated that there was no difference in the ratio of the oxygen consumed to the oxygen delivered (consumption oxygen/delivery oxygen) between the two groups despite a significant difference for the delivery oxygen between the two groups. The ratio was about 0.54 in both groups.

In our study, the delivery oxygen was 0.202 ± 0.069 mL of O_2/min/100 g of left ventricle for group C and 0.521 ± 0.071 mL of O_2/min/100 g of left ventricle for group FC. If the consumption oxygen was 54% of the delivery oxygen, it would be 0.109 ± 0.037 mL of O_2/min/100 g of left ventricle for group C and 0.281 ± 0.038 mL of O_2/min/100 g of left ventricle for group FC. The metabolic requirement of the heart has been reported to be 0.43 mL of O_2/min/100 g of left ventricle at 25°C, 0.27 mL of O_2/min/100 g of left ventricle at 15°C, and 0.13 mL of O_2/min/100 g of left ventricle at 5°C [11]. In group FC, the oxygen consumption met this demand and aerobic metabolism could be maintained. Only 2 mol of ATP are produced for every mole of glucose in anaerobic metabolism; however, 38 mol of ATP are produced in aerobic metabolism. Therefore, aerobic metabolism is essential to preserve levels of ATP and myocardial viability. We believe that provision of an adequate oxygen supply was one of the major factors that contributed to the improved preservation of hearts in group FC as opposed to group C.

Osmotic or Oncotic Pressure

Myocardial edema is a frequent consequence of ischemic damage. To keep the fluid within the vascular spaces, the perfusate must have sufficient osmotic or oncotic pressure. The ideal osmotic pressure has been reported to be 300 mosm/L by Hearse and associates [12] and 460 to 480 mosm/L by Thomas and colleagues [13]. In the present study, the osmolarity of the perfusate was 380 to 400 mosm/L in group C and 330 to 350 mosm/L in group FC. The perfusate used in group FC contained oncotic pressure, but the perfusate used in group C did not. Though the ideal oncotic pressure has not yet been established, abnormal ultrastructural appearance was less in group FC than group C. It is believed that the reasons for this were the preservation of the cell volume–regulating mechanism because an adequate level of ATP was maintained and because of the presence of oncotic pressure in the perfusate of group FC [7, 10].

Perfusate

POTASSIUM. The ideal potassium concentration has not been established. It has been reported that the potassium concentration should not exceed 40 mEq/L because higher levels of hyperkalemia alter cell membrane permeability so that extracellular calcium flows into the cell and raises energy requirements [14]. However, other reports have stated that the potassium concentration in the perfusate should be similar to that in the intracellular fluid because the sodium-potassium pump is inactive at temperatures lower than 10°C and therefore the gradient between intracellular and extracellular potassium concentration is not regulated [13, 15]. In this study, the potassium concentration was 23 mEq/L in both groups.

CALCIUM. A calcium-free perfusate leads to "calcium paradox [16]" as a result of altered membrane permeability to calcium during reperfusion, and a perfusate with a high calcium concentration causes systolic arrest known as "stone heart" [17] and myocardial damage. Amano [18] showed that the optimum calcium concentration of cardioplegia was 2 mEq/L. In this study, the calcium concentration of the perfusate was 1.3 mEq/L in both groups.

MAGNESIUM. Magnesium is predominantly an intracellular ion. It is a vital cofactor in various enzyme reactions and also protects the myocardial mitochondria.

Perfusion Pressure

If the perfusion pressure is lowered, the oxygen supply to the myocardium will also decrease. A high perfusion pressure can cause damage to the capillary beds, which leads to myocardial edema. Many investigators have maintained perfusion pressure at 5 to 20 mm Hg [5, 6]. In this study, to supply as much oxygen as possible, the perfusion pressure was maintained at 20 mm Hg. During the 24-hour preservation, the coronary flow showed no remarkable changes in either group.

Hypothermia

The lower the perfusion temperature, the lower the energy requirements. However, even at temperatures of less than 0°C, metabolic activity still takes place, and freezing injury occurs at temperatures lower than 0°C. Many investigators have kept the temperature between 4° and 7°C [6, 19]. However, it has been reported that 15°C is the optimal temperature [20]. A consensus on the ideal temperature of the perfusate has not yet been established.

Alkalinity

Many studies indicate that the pH of the perfusate should be kept at the "normal" level of 7.40. Mendler and associates [6] reported that the ideal pH is 7.40. It is well known that the neutral point of water is temperature dependent and rises as the temperature increases because of changes in the ionization constant (Δ pH/°C = 0.015). Becker and associates [21] demonstrated that lactate metabolism remained normal and that left ventricular performance returned to its preischemia level when the pH was adjusted to produce relatively alkalinity. The ideal pH was reported to be 8.0 to 8.1 at 17°C by Buckberg [7]. In our study, pH was kept at 8.0 at 4°C.

Evaluation of Preserved Heart Viability

An indicator of preserved heart viability has not yet been established. During long-term preservation, the initial phase of functional deterioration in ischemic myocardium is characterized by a decrease in compliance rather than contractility. In group FC, neither compliance nor contractility decreased significantly. The amount of released CK was reported to be a good indicator of the viability of the preserved heart by Mendler and co-workers [6]. In group FC, the amount of CK released into the perfusate was significantly lower than in group C. Badenhamer and associates [10] demonstrated that increased myocardial water content is related to decreased levels of ATP. In group FC, myocardial edema was significantly lower than in group C, thus suggesting that ATP levels were well preserved in group FC.

Conclusion

We conclude that in 24-hour preservation of the isolated canine heart by continuous hypothermic low-pressure coronary perfusion, the use of fluorocarbon emulsion as an oxygen carrier is beneficial for myocardial protection. The major factors responsible for the excellent viability of hearts preserved with fluorocarbon emulsion are adequate oxygen supply and oncotic pressure in the medium.

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Valve Replacement in the Octogenarian

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Twenty-five patients (11 men and 14 women) aged 80 to 88 years (mean age, 82 years) underwent valve replacement at St. Louis University from August 1980 to June 1988. Isolated valve replacement was performed in 11 patients. Combined procedures included valve replacement with myocardial revascularization (7 patients), multiple valve procedures (5 patients), and ascending aortic plication (2 patients). Fifteen patients (60%) were in New York Heart Association functional class III and 10 (40%) were in class IV preoperatively. The operative mortality was 20% and late mortality was 20% (mean follow-up, 36 months). Isolated valve replacement carried a 9% early and 0% late mortality, whereas combined procedures of any type had a 16% early and 20% late mortality. Only 7 patients (28%) had a completely uncomplicated postoperative hospitalization. Twenty patients were discharged after a mean hospital stay of 18 ± 16 days. Their mean New York Heart Association functional class was 1.6 ± 0.66. The 1-year and 2-year actuarial survival rate is 79% and 69%, respectively. A significant increase in operative mortality is seen when valve replacement is combined with myocardial revascularization or an additional valve procedure. Late clinical improvement, as judged by return to an independent lifestyle, justifies this approach for select patients.

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The number of people 80 years of age or older in the American population is increasing [1]. In 1980, the US Bureau of Census [2] reported that 43% of all Americans will reach the age of 80 years and live an average of nearly 8 more years. Approximately 40% of all octogenarians have symptomatic heart disease, and some will be candidates for valve operations [3].

Over the last two decades, there has been a decrease in the morbidity and mortality of operation for valvular heart disease. This improvement is due to better myocardial preservation, continued refinement of surgical techniques, and improvement in valve prostheses. Notwithstanding, there continues to be a delay in referral of aged patients with valvular disease until the pathological process has progressed to an advanced state. Several recent studies [4, 5] have reported excellent results in cohorts of septuagenarians undergoing valve operations. Based on this success, surgeons are now undertaking valve operations in patients over the age of 80 years. To determine the efficacy of valve replacement in the octogenarian, we reviewed the course of our operative patients 80 years of age or older with regard to morbidity, mortality, postoperative function, and longevity.

Patients and Methods

During the period of August 1980 to June 1988, 28 valve operations (aortic valve replacement, 12; mitral valve replacement, 8; combined aortic and mitral repair or replacement, 5) were performed in 25 patients 80 years old or older at St. Louis University Hospital and St. Mary's Health Center. The data abstracted from a retrospective review of patient records included age, sex, race, admitting diagnosis, cardiac risk factors, procedure performed, and postoperative complications. Angina was graded using the Canadian Cardiovascular Society classification. A New York Heart Association (NYHA) functional classification was assigned to each patient. Congestive heart failure was considered to be present if both digitalis and diuretic drugs were being used and rales were described on physical examination. Each patient was evaluated by an attending cardiologist and surgeon. Operation was undertaken when both physicians concluded that no alternative therapy was advisable or technically feasible. Patients with severe central nervous system dysfunction or disabling noncardiac problems that prevented a semiindependent lifestyle were not considered operative candidates.

Cardiac catheterization was performed in all patients. Regional wall motion abnormality was measured by left ventricular score (as defined by the Coronary Artery Surgery Study), whereas ventricular function was assessed using left ventricular end-diastolic pressure and cardiac index. The degree of valve stenosis or insufficiency was quantitated using standard catheterization techniques. Critical coronary artery stenosis was defined as greater than 50% occlusion for the left main coronary artery and greater than 70% for other coronary arteries.

The operative technique consisted of a standard median sternotomy, routine aortic and right atrial cannulation, and nonpulsatile systemic hypothermic (30°C) cardiopulmonary bypass. Disposable membrane oxygenators were primed with crystalloid solution and albumin. Intermit-

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tent cold hyperkalemic blood cardioplegia (6°C) and topical myocardial cooling were employed for myocardial protection. The conduit for coronary artery bypass grafting was always the saphenous vein.

Postoperative data recorded included time until discharge after operation, operative mortality (death within 30 days or at any time during the initial hospitalization), and complications. Patients discharged from the hospital were considered early survivors. Late mortality is defined as the number of patients who were dead at the time of follow-up study (June 1988) divided by the total number of hospital survivors. Additional information was obtained by contact with the patient, the patient's physician, or both. The level of physical activity (NYHA functional classification) and intervening hospitalization or complication were also determined.

Univariate analysis of continuous variables was performed using Student's t test. A p value of 0.05 was considered significant. Mean values are expressed as plus or minus the standard deviation. The actuarial survival rate of the 20 hospital survivors was calculated by the Kaplan and Meier technique. The standard error of the mean as it relates to the actuarial survival was derived according to Peto and co-workers [6].

Results

This group of octogenarians consisted of 11 men and 14 women, whose mean age at operation was 82.0 years (range, 80 to 88 years). All patients had congestive heart failure preoperatively, with a mean NYHA functional class of 3.4 ± 0.3. None of the patients required preoperative institution of intravenous nitroglycerin, inotropic agents, or intraaortic balloon counterpulsation. Nineteen patients underwent left ventriculography. The mean left ventricular score and end-diastolic pressure were 6.7 ± 2.8 and 18.3 ± 10.9 mm Hg, respectively. The mean cardiac index measured in 15 of these patients was 2.2 ± 0.5 L/min/m^2. The mean aortic valve gradient in 16 patients with aortic stenosis was 79.3 ± 30.8 mm Hg. Mitral valve incompetence was demonstrated in 11 patients. The mean degree of valvular insufficiency was 2.6 ± 1.2 on a scale of 0 to 4.

Table 1. Preoperative Diagnosis and Operative Treatment

Diagnosis	No. of Patients[a]	Operation
Aortic valve disease	12 (48)	AVR (n = 6)
		AVR-CABG (n = 4)
		AVR-aortic plication (n = 2)
Mitral valve disease	8 (32)	MVR (n = 5)
		MVR-CABG (n = 3)
Combined valvular disease	5 (20)	AVR-MVR-CABG (n = 3)
		AVR-MVA-CABG (n = 1)
		AVR-MVA (n = 1)

[a] Numbers in parentheses are percentages.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVA = mitral valve annuloplasty; MVR = mitral valve replacement.

Table 2. Results of Operation

Operation	No. of Patients	Early Deaths[a]	Late Deaths
AVR	6	. . .	. . .
AVR, CABG	4	1 (25)	2
AVR and ascending aortic plication	2	1 (50)	. . .
AVR, MVA	1	. . .	. . .
AVR, MVR, CABG	3	1 (33)	1
AVR, MVA, CABG	1	. . .	1
MVR	5	1 (20)	. . .
MVR and CABG	3	1 (33)	. . .
Total	25	5	4

[a] Numbers in parentheses are percentages.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVA = mitral valve annuloplasty; MVR = mitral valve replacement.

Table 1 lists the diagnoses and operative procedures. The cause of aortic valve disease was rheumatic in 1 patient, congenital in 3 patients, and degenerative in 13. The cause of the mitral valve disease was ischemic in 1 patient, rheumatic in 7 patients, and myxomatous in the remaining 5 patients.

Hemodynamically significant coronary artery disease was present in 14 patients (56%). Single-vessel disease was documented in 7 patients, double-vessel disease in 3, triple-vessel disease in 3, and left main stenosis in 1. Nine patients (36%) experienced angina preoperatively and had a mean angina class of 3.4 ± 0.8.

The Carpentier-Edwards bioprosthesis was used in all but 2 patients, in whom the Björk-Shiley valve was employed. Concomitant procedures performed included coronary bypass grafting in 12 patients (48%), plication of an ectatic ascending aorta in 2, aortic annulus enlargement utilizing autologous pericardium in 4, and mitral valve annuloplasty in 2. The primary indication in all combined procedures was valvular disease. The mean number of distal anastomoses was 1.7 per patient in the 12 patients having revascularization.

The operative mortality is shown in Table 2. There were five hospital (early) deaths (20%). Two patients had undergone aortic valve replacement with coronary artery bypass grafting for critical aortic stenosis with congestive heart failure. Plication of an ascending aortic aneurysm was also performed in 1 of these patients. Both patients had left ventricular end-diastolic pressure greater than 30 mm Hg and a cardiac index of less than 1.8 L/min/m^2 preoperatively. Neither patient could be removed from cardiopulmonary bypass despite the use of inotropic agents and intraaortic balloon counterpulsation. The third death occurred in a patient in NYHA class IV with mitral regurgitation and triple-vessel coronary artery disease. He died from low cardiac output 24 hours after mitral valve replacement with two coronary artery bypass grafts. The fourth patient had bilateral asymptomatic carotid stenosis and underwent isolated mitral valve replacement, but died at 3 days after a cerebrovascular accident. The

Table 3. Postoperative Complications

Complication	No. of Patients[a]
Atrial arrhythmias	7 (35)
Permanent CVA	5 (25)
Reversible CVA	3 (15)
UTI	3 (15)
Renal failure	2 (10)
Prolonged ventilation (>48 hours)	2 (10)
Hemothorax	1 (5)
Ventricular ectopy	1 (5)
Sepsis	1 (5)
Candida sepsis	1 (5)
Pacemaker	1 (5)
Total	27

[a] Numbers in parentheses are percentages.

CVA = cerebrovascular accident; UTI = urinary tract infection.

remaining early death occurred in a patient undergoing aortic and mitral valve replacement with coronary artery bypass grafting. He never fully regained consciousness, dying 14 days postoperatively from multiorgan system failure.

Four late deaths occurred among 20 hospital survivors. One patient developed bacterial pneumonia 1 month after aortic valve replacement and single vein coronary artery bypass grafting. He died several weeks later of multiple complications including gastrointestinal bleeding, acute renal failure, and systemic candidiasis. The remaining 3 patients died at 35 days (aortic valve replacement, mitral valve replacement, coronary artery bypass grafting), 4 months (aortic valve replacement, mitral valve annuloplasty, coronary artery bypass grafting), and 13 months (aortic valve replacement, coronary artery bypass grafting) postoperatively after complications of cerebrovascular accidents. The first 2 of these 3 patients sustained their neurological deficit at the time of valve replacement. The third patient had a primary cerebrovascular accident more than 1 year after operation.

There were a variety of complications in the 20 patients who survived operation (Table 3). New atrial fibrillation or atrial flutter developed in 7 patients (28%). Complete heart block developed in 1 patient with preoperative left bundle-branch block after mitral valve replacement with coronary artery bypass; this patient required a permanent transvenous pacemaker. Acute renal failure requiring dialysis developed in 2 patients (10%). Five patients (25%) sustained a permanent stroke, and transient neurological dysfunction was observed in 3 additional patients (15%). Prolonged ventilator support was required in 2 patients (10%). The remaining nonfatal complications included urinary tract infections in 3 patients (15%), ventricular ectopy in 1 (5%), and a hemothorax in the remaining patient (5%). Common minor problems included confusion, anorexia, nausea, and delay in ambulation. No patient experienced a wound infection or required reoperation for postoperative bleeding, sternal infection, or dehiscence.

The 20 operative survivors had a mean postoperative hospital stay of 18 ± 16 days. No patients were lost to follow-up, which ranged from 7 to 85 months (mean follow-up, 36 months). Each of these long-term survivors is active; only 1 patient resides in a nursing home. The NYHA functional class in this group has improved from 3.5 ± 0.5 to 1.6 ± 0.66 ($p < 0.001$). All hospital survivors improved at least one NYHA functional class. The actuarial survival at 1 and 2 years is 79% and 69% with an estimated standard error of the mean of ±0.10 and ±0.12, respectively.

Comment

There has been an understandable conservatism about offering octogenarians valve replacement because of advanced age and frequent associated medical problems. In the last 5 years, this pessimistic philosophy has changed as a result of improvements in extracorporeal perfusion, valve prostheses, perioperative care, and myocardial protection. A number of reports [7, 8] have evaluated the results of valve replacement in patients over the age of 70 years. The perioperative mortality has ranged from 3% to 30% for isolated valve replacement and from 10% to 50% for multiple valve replacement or combined procedures [7, 8]. It has been concluded that cardiac operations can be performed with an elevated but acceptable risk in this advanced age group.

Reports [9–13] have recently appeared, confirming the safety and efficacy of open heart operations in the octogenarian. The majority of these patients underwent isolated coronary artery bypass grafting. To our knowledge, no report has focused on the subgroup of octogenarians undergoing valve replacement.

Our early mortality of 20% and overall mortality of 36% are higher than those reported for septuagenarians, but are similar to those reported by Tsai and associates [12] for their octogenarian population (21% and 31%, respectively). Edmunds and associates [13] recently reported on a series of 100 octogenarians undergoing cardiac operations, 58% of whom had valve replacement. In their report the early mortality for valvular operations was 31%, with an overall mortality of 52%.

Isolated valve replacement in our patients resulted in a 9% (1/11) early mortality with no late deaths at follow-up study to 88 months. All patients are functional and living at home, a fact that suggests that isolated valve replacement is safe and efficacious and should be pursued aggressively in the octogenarian.

Patients undergoing more than isolated valve replacement did not fare as well. In our series, multiple valve replacement or repair resulted in a 20% early and 50% late mortality. These procedures required prolonged periods of extracorporeal circulation and global ischemia, both of which are poorly tolerated by these patients with limited cardiac reserve. In those for whom the decision is made for surgical intervention, efforts must be made to keep the operation simple and expeditious. Mitral valve repair may be preferable to replacement to better preserve left ventricular function in properly selected patients.

Single valve replacement combined with coronary artery bypass grafting resulted in a 28% early and a 40% late mortality. This is noticeably higher than the 17% early mortality reported by Borkon and co-workers [14] in septuagenarians undergoing similar combined procedures. This elevated mortality brings to question the necessity for concomitant revascularization during valve replacement in this elderly subset. Conventional practice suggests that revascularization should be performed at the time of valve replacement if major coronary artery stenosis is present regardless of the presence or absence of angina [15]. Reports [16] in younger patient populations indicate that myocardial revascularization does not increase the operative mortality of valve replacement, and the functional result may be improved by relieving the symptoms of angina pectoris and providing improved myocardial protection. This aggressive approach requires prolonged ischemic time and may not be appropriate in the octogenarian. Three of our five early deaths were due to low cardiac output in patients having combined valve replacement and coronary artery bypass grafting. All 3 had marked left ventricular dysfunction preoperatively with little or no angina, and might have been better served by valve replacement alone. We now believe that in octogenarians, only those with critical (>80%) coronary lesions or severe angina should undergo concomitant coronary bypass grafting. Less than complete revascularization is an acceptable alternative in this elderly subset of patients when congestive heart failure is a primary indication for operation.

We currently believe the bioprosthetic valve is the safest cardiac valve substitute in the octogenarian. A recent report by Jamieson and associates [17] states that structural deterioration of tissue valves is limited in the elderly population. Because systemic anticoagulation is rarely required, bioprosthetic valves have a reduced incidence of hemorrhagic and thrombotic complications compared with mechanical valves [14].

Several series [18, 19] have reported a high incidence of postoperative complications in elderly patients. Our experience confirms this, as evidenced by only 28% (7/25) of our patient population having an entirely uncomplicated hospital course. Particularly frequent were problems involving the central nervous system. Thirty-two percent of our patients suffered some neurological or mental impairment (delirium, confusion, or stroke) after operation. In this fragile patient subset, a stroke resulting in permanent and serious paresis is a catastrophic event, which is always incapacitating and often fatal. In our series, all 5 patients sustaining a cerebrovascular accident died from related complications. These patients account for 55% of the deaths in this series.

Our experience with isolated valve replacement in the octogenarian justifies an aggressive surgical approach in these patients. Valve replacement combined with coronary artery bypass grafting in this subset warrants a more conservative posture. Although an operation can be undertaken, both physician and patient must fully understand the magnitude of operative risk. Our 60% overall mortality for double valve procedures suggests that valve replacement for these patients may be contraindicated. Open decalcification of the aortic valve using ultrasonification and reconstruction of the mitral valve may prove to be reasonable alternatives to implantation of prostheses in this fragile patient subset.

Symptomatic medical treatment may do little to improve the condition of elderly patients with severe valvular heart disease. Once the symptoms of congestive heart failure develop, the quality of life deteriorates substantially. In the past, these individuals were not offered valve replacement because of unacceptably high perioperative mortality and morbidity. The improvement in functional capacity and the prolongation of late survival in our series justify valve replacement in select octogenarian patients. The operative risk is related to the procedure performed, as well as the degree of cerebrovascular, renal, and respiratory impairment present preoperatively. Age alone should not be considered a contraindication to valve replacement.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 4, 1990. The closing date for registration is August 1, 1989.

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Embryonic Versus Adult Myocardium: Adenine Nucleotide Degradation During Ischemia

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Neonatal myocardium demonstrates better recovery from ischemia than does adult tissue. We tested the hypothesis that developmental differences in adenine nucleotide degradation might facilitate recovery by quantitating depletion of high-energy phosphates in nine-day-old embryonic (n = 9) and 15-month-old adult (n = 14) chicken hearts at 15-, 30-, 45-, and 60-minute intervals of normothermic ischemia in vitro. Nucleotides adenosine triphosphate, adenosine diphosphate, and adenosine monophosphate and nucleosides adenosine, inosine, hypoxanthine, and xanthine were determined by high-performance liquid chromatography. Several observations in metabolite degradative response to ischemia were noted. The embryonic myocardium maintained higher adenosine triphosphate and adenosine monophosphate levels over the course of the investigation than did mature myocardium. Moreover, the adult group showed an increase in diffusible nucleoside pool metabolites. Relative immaturity of enzymes responsible for nucleotide degradation may facilitate postischemic recovery by preserving nondiffusible high-energy phosphate precursors to participate in salvage resynthesis of adenosine triphosphate.

(Ann Thorac Surg 1989;48:109–12)

Considerable research has been dedicated to optimize methods of intraoperative cardiac protection. Failure to maximize protective maneuvers is in part due to limited understanding of the biochemical derangements associated with global ischemia [1–5]. In the postischemic period, depletion of adenine nucleotide pools has been associated with subsequent cardiac dysfunction [6].

High-energy phosphate utilization during ischemia has been correlated with postischemic recovery of cardiac function [7]. A prediction of physiological recovery can be made by quantitating useful total adenine nucleotide pools as coupled with total diffusible purine pools. In theory, by accumulating salvageable products of metabolism (compounds remaining within the cell, and thus retaining the capacity for adenosine triphosphate [ATP] resynthesis), damaged tissue is better able to resume normal levels of function during periods of reperfusion.

Previous investigators [8] observed that functional recovery from ischemic insult in neonatal hearts was superior to that of adult hearts. Specifically, after 30 minutes of normothermic ischemia in the canine neonate, functional recovery was excellent, with aortic flow and cardiac output at levels greater than 90% of control levels [7]. In contrast, a similar ischemic interval in adult hearts resulted in profound injury and severe limitation of recovery [9].

Although many factors may be responsible for these findings, examining different patterns of high-energy phosphate depletion during ischemic injury might provide some insight into age-related tolerance to ischemia. Investigations from our laboratory [10] have demonstrated species- and age-related differences in myocardial adenine nucleotide catabolism during ischemia. Certain observations characterized differences between canine neonatal and canine adult myocardial accumulations of adenosine monophosphate (AMP) during ischemia [10]. Interestingly, the neonatal group showed increased accumulations of AMP over a 60-minute interval of ischemia.

Notably, within certain groups, neonatal myocardium has proved better able to recover useful metabolic compounds after a given interval of ischemic injury. Studies [8] have demonstrated species-related differences in AMP accumulation during ischemia. Canine and lamb neonates have shown substantial accumulations of AMP, whereas neonatal rats demonstrated gradual degradation of AMP during periods of ischemia (Fig 1) [8].

We tested the hypothesis that there were developmental differences in adenine nucleotide degradation by comparing the effects of ischemia on embryonic and adult avian myocardium. We wished to characterize age-related differences in high energy phosphate degradation in this model. Moreover, we hoped to further our understanding of developmental biochemistry by examining extremes of ages.

Material and Methods

Fertilized eggs and adult White Leghorn chickens were obtained from Featherdown Farms, Apex, NC. Eggs were placed in a humidified 37°C incubator. All investigations were conducted according to the guidelines of the American Physiological Society. The animals were treated with care as suggested in the National Society of Medical Research publication *Principles of Laboratory Animal Care.*

Fourteen adult chicken hens weighing 2.5 to 3.7 kg were studied. Each was intravenously anesthetized with

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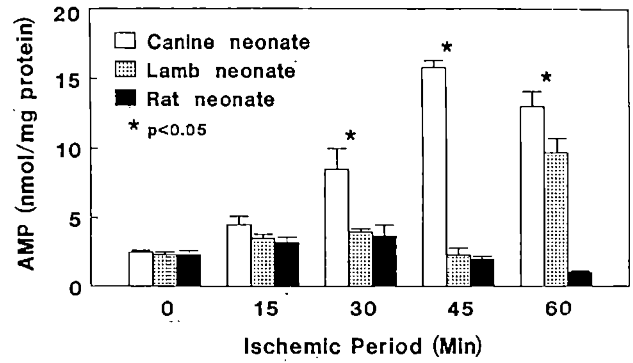

Fig 1. Comparison of the accumulation of AMP for three species during periods of ischemia. The canine and lamb neonate show greater levels of the metabolite AMP during intervals of ischemia than does the rat neonate. Data are shown as the mean ± the standard error of the mean.

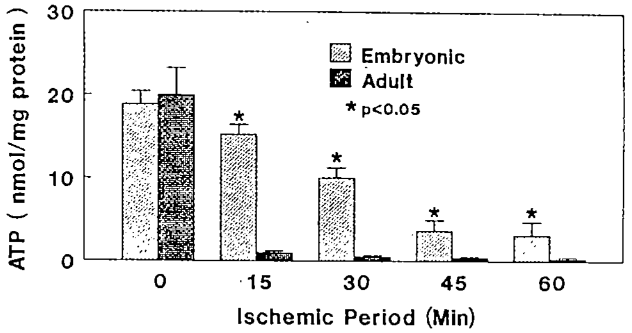

Fig 2. The embryonic avian group was better able to retain levels of adenosine triphosphate (ATP) compared with the adult group during periods of ischemic injury. Data are shown as the mean ± the standard error of the mean.

10.5 mg/kg of sodium pentobarbital and connected to a Harvard 607A ventilator supplying a 95% oxygen/5% carbon dioxide mixture. A left thoracotomy was performed, and the pericardium was opened. After a stabilization period, a liquid nitrogen–cooled Tru-cut needle biopsy was performed. The heart was rapidly excised and subjected to normothermic ischemia by placing it in a sealed, airtight container submerged in a 37°C water bath.

Nine nine-day-old chicken embryo hearts were rapidly excised and subjected to periods of normothermic ischemia by placing left ventricular biopsy samples in airtight, sealed containers submerged in a 37°C water bath. Individual biopsy samples were taken at 15, 30, 45, and 60 minutes of ischemia and placed in liquid nitrogen. Each specimen was extracted in 12% trichloroacetic acid at 4°C for 30 minutes. The solute was separated from denatured proteins by centrifugation and neutralized with a 2:1 (vol/vol) tri-*n*-octylamine/freon solution.

Levels of the nucleotides ATP, adenosine diphosphate (ADP), and AMP and the nucleosides adenosine, inosine, hypoxanthine, and xanthine were analyzed by high-performance liquid chromatography. Protein determinations were performed on a Gilford spectrophotometer [11]. Data are given as mean ± standard error of the mean. The values were compared using paired Student's *t* tests. Differences were considered significant if the probability (*p*) value for comparison of least squares means was less than 0.05.

Results

We found differences in high energy phosphate metabolism between embryonic and adult myocardium. Embryonic avian myocardium demonstrated a slower depletion of ATP than did adult avian myocardium. Levels for the embryonic tissue began at 18 nmol/mg protein and tapered at end-ischemia to 4 nmol/mg protein. The adult group demonstrated rapid depletion of ATP, beginning at 20 nmol/mg protein and decreasing to levels less than 1 nmol/mg protein (Fig 2). Embryonic avian myocardium showed an unusual accumulation of AMP during periods of ischemia. The embryonic group progressed from a value of 2.0 nmol/mg protein to a value of 10.5 nmol/mg protein at the 60-minute ischemic point. In contrast, the adult hearts showed early AMP accumulation, with subsequent rapid depletion (Fig 3).

The next metabolite in the pathway, adenosine, accumulated rapidly in the adult group, but gradually in the embryonic group (Fig 4A). The adult animals demonstrated early accumulation of inosine; this was maintained for the duration of our measurements, whereas the embryonic groups showed slower accumulation (Fig 4B). In the adult group, hypoxanthine levels were noted to be significantly elevated compared with the embryonic model, which had only marginal accumulation (Fig 5A). The adult group had significant levels of xanthine, whereas the embryonic group failed to accumulate xanthine (Fig 5B).

The total adenine nucleotide pool for the two groups was similar during the stabilization period. Gradual differences were noted over the course of the ischemic intervals. The embryonic group had significant persistence of the total adenine nucleotide pool, with the level after 60 minutes of ischemia being 52% of the control value. The adult group retained only 14% of its initial value (Fig 6A). The total diffusible pool increased signifi-

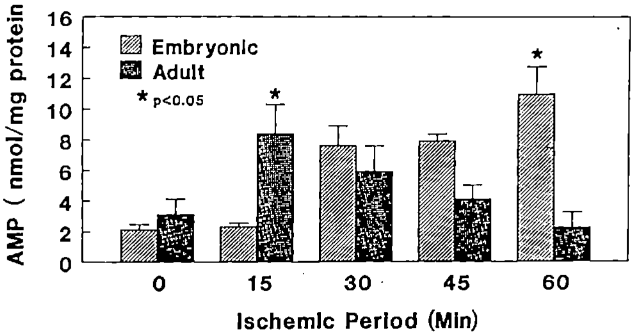

Fig 3. The adult group demonstrated an early accumulation with rapid depletion of adenosine monophosphate (AMP), whereas the embryonic group progressed from a value of 2.0 nmol/mg protein to a level of 10.5 nmol/mg protein at the end of 60 minutes of normothermic ischemia. Data are shown as the mean ± standard error of the mean.

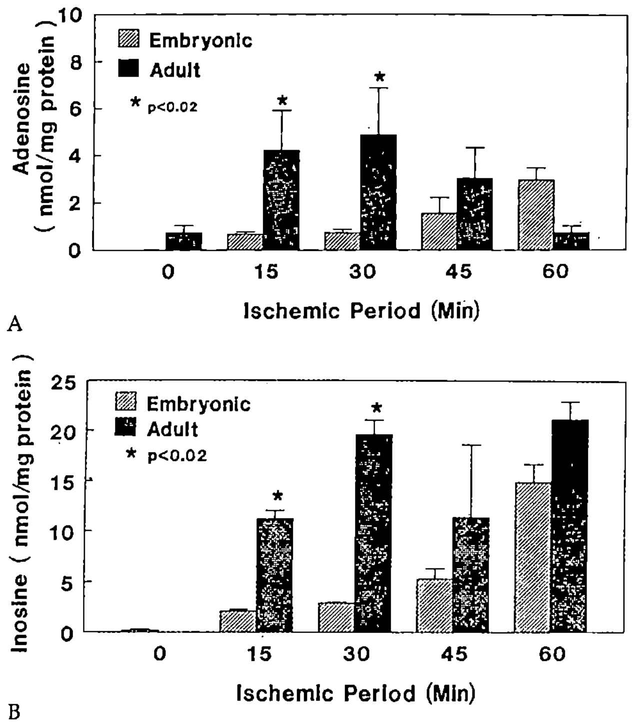

Fig 4. The accumulation of adenosine (A) and inosine (B) in the adult group was greater than that in the embryonic group. Data are shown as the mean ± the standard error of the mean.

cantly in the adult group to levels well above those of the embryonic group (Fig 6B).

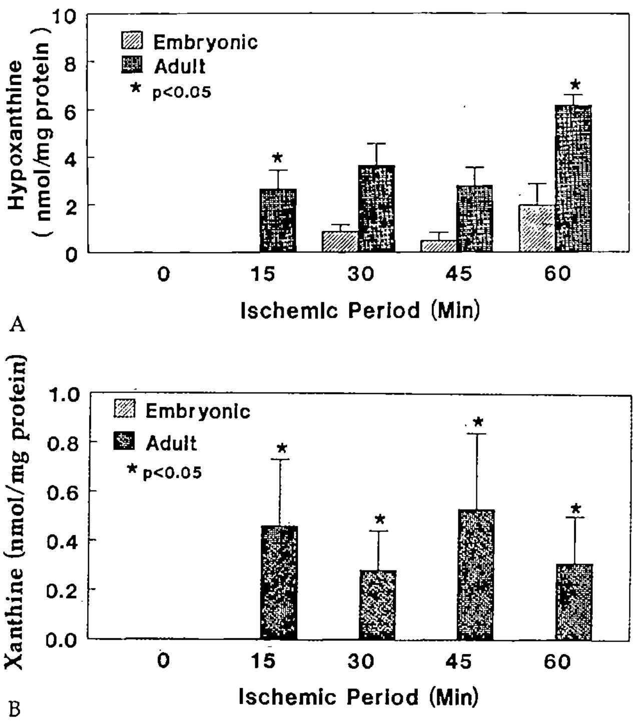

Fig 5. The embryonic group had significantly less accumulation of the end metabolites hypoxanthine (A) and xanthine (B). Data are shown as the mean ± standard error of the mean.

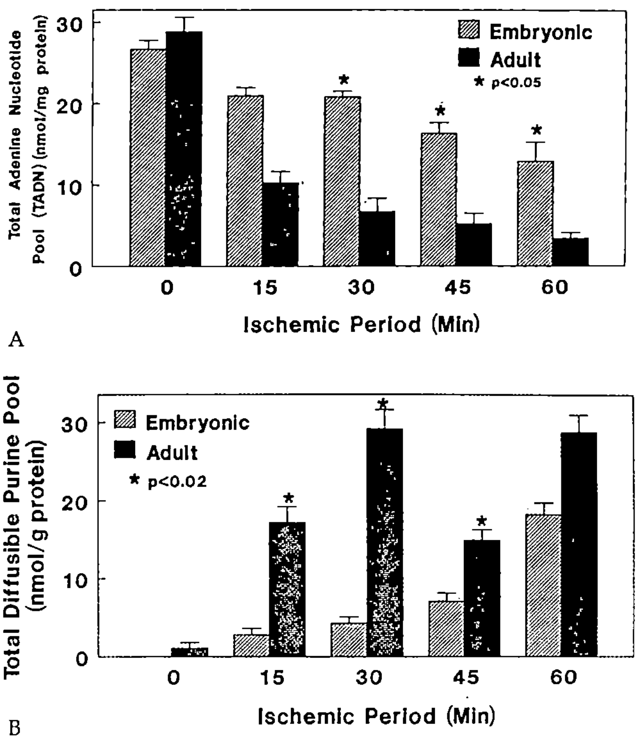

Fig 6. (A) The total adenine nucleotide pool showed a slower depletion in the embryonic group. At the end of 60 minutes of ischemia, the adult group level was 14% of the control level compared with 52% of the control level for the embryonic group. (B) The total diffusible purine pool accumulated rapidly in the adult group compared with the embryonic group.

Comment

This investigation analyzed adenine nucleotide catabolism in myocardium subjected to ischemia in two extremes of development. We noted a slow rate of ATP depletion, greater retention of the total adenine nucleotide pool, and less total diffusible pool accumulation in embryonic compared with adult myocardium. Of significance in our study is the marked accumulation of AMP in the embryonic myocardium. A possible mechanism is immaturity of 5′ nucleotidase, which is largely responsible for AMP catabolism.

Recently, investigators have sought to categorize age-related differences in myocardial response to ischemia. The present data demonstrate age-related differences in avian high-energy phosphate metabolism. Relative immaturity of enzymes responsible for nucleotide degradation may facilitate postischemic recovery by preserving nondiffusible high-energy phosphate precursors to participate in salvage resynthesis of ATP. This work characterizes adenine nucleotide metabolism for embryonic and adult chicken hearts. If the myocardial total adenine nucleotide pool is important for metabolic and contractile recovery after ischemia, maintaining this pool is essential.

Further work would enhance the present investigation. The characterization of embryonic and adult myocardial enzyme kinetics might disclose reasons for the observed differences in high-energy phosphate degradation during ischemia. Identification of mechanisms that maximize preservation would be advantageous. Moreover, ways of achieving this goal might be recognized if discrepancies between high-energy phosphate utilization among different age groups and within varying species prove to relate significantly to postischemic recovery.

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We thank Robert L. McRae for his efforts and energies. We also give special thanks to Marlon Sellers for his continued support.

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Primary Endobronchial Granular Cell Myoblastoma

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Granular cell myoblastoma is a common lesion of uncertain histogenesis. It commonly affects the tongue, breast, and subcutaneous tissues. However, its occurrence in the tracheobronchial tree is rare. Although generally a benign lesion, isolated malignant granular cell myoblastoma as well as its coexistence with other primary bronchogenic carcinomas has been documented. In spite of recent anecdotal reports advocating endoscopic removal of this lesion, we believe definitive surgical excision is a more rational choice of treatment.

(Ann Thorac Surg 1989;48:113–5)

Granular cell myoblastoma (GCM) is a benign tumor of ubiquitous anatomical distribution. The most frequent sites of occurrence are the tongue, breast, and subcutaneous tissues. Other less common sites of occurrence include the larynx, esophagus, mediastinum, retroperitoneum, myocardium, and biliary tree. Its occurrence within the tracheobronchial tree as a primary lesion is rarely reported. The presenting symptoms of bronchial GCM such as cough, recurrent pneumonia, pleuritic pain or hemoptysis, and a mass lesion of the lungs on chest roentgenograms are similar to those of primary bronchogenic tumors, making it difficult at times to differentiate between them.

A 45-year-old black woman was seen in consultation for productive cough, exertional dyspnea, and right-sided pleuritic pain of 2 months duration. Medical history included cigarette smoking of one pack a day for 30 years. Chest roentgenograms showed a mass lesion of the right upper lobe, which was confirmed by a computed tomographic scan of the thorax.

On admission to the hospital, physical examination was entirely unremarkable except for diminished breath sounds over the right upper lung field. Her admission complete blood count, serum electrolyte levels, and arterial blood gases on room air were all within normal limits. Several sputum samples had a normal acid-fast bacillus smear and were negative for bacterial and fungal growth. Cytology was negative for malignant cells.

A flexible bronchoscopy was performed under general anesthesia before thoracotomy. The trachea and the left tracheobronchial tree were normal. The orifice of the right upper lobe bronchus was distorted by a 1 × 1-cm grayish yellow submucosal lesion. A mediastinoscopy was performed after bronchoscopy, revealing no obvious subcarinal or paratracheal lymphadenopathy. The patient then underwent a right posterolateral thoracotomy. The right upper lobe appeared grossly abnormal with consolidation and fibrotic changes. A right upper lobectomy was performed. Frozen section of the bronchial stump was free from tumor. Pathology sections of the right upper lobe showed an obstructing lesion of the proximal bronchus with large polygonal cells containing finely granular eosinophilic cytoplasm and small dark vesicular nuclei consistent with benign granular cell myoblastoma (Fig 1). There was marked bronchiectasis with acute and chronic inflammatory changes of the right upper lobe parenchyma. All 12 lymph nodes from the right hilar and paratracheal area were free from tumor. The patient recovered well postoperatively and was discharged on postoperative day 7. She returned to work 6 weeks later and continued to do well 12 months after operation.

Comment

Granular cell myoblastoma was first described by Abrikossoff [1] in 1926. The first case of primary endobronchial GCM was reported by Kramer [2] in 1939, and by 1978 only 47 cases had been reported [3]. Between 1978 and 1987, 20 more cases were added to the English-language literature, bringing the total to 68 with this report.

Granular cell myoblastoma commonly occurs in the third or fourth decade of life, with the youngest reported patient being a 5-year-old child [4]. It seems to have a predilection for the black population, possibly because of the greater reactive potential of mesenchymal tissues in this group. An even distribution of GCM among both sexes has been observed. Cigarette smoking is a frequent but not constant finding in the reported cases. Although polycentric endobronchial GCM was thought to be rare by earlier authors, a recent review of the literature demonstrated a 13.3% incidence of polycentricity either within the same side or bilaterally [5]. The incidence of multiple organ involvement is about 15.9% [6].

The traditional myogenic origin of granular cell tumors as proposed by Abrikossoff [1] was convincingly challenged in 1950 by Pearse [7], who identified cytoplasmic granules that contained protein and high concentrations of cerebrosides and gangliosides, suggesting a neural

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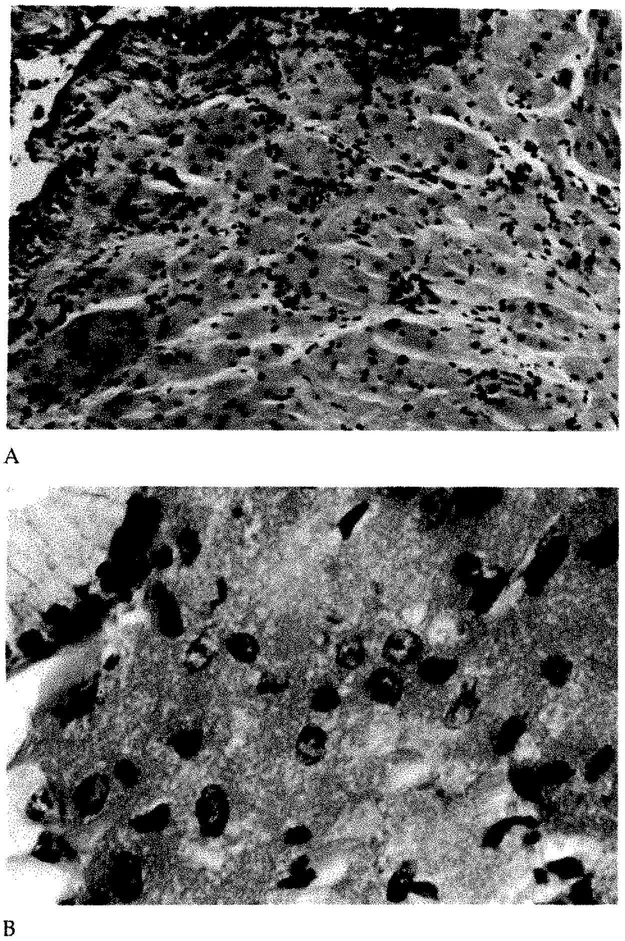

Fig 1. (A) Photomicrograph showing granular cell myoblastoma cells with eosinophilic granular cytoplasm arranged in cords. (Hematoxylin and eosin, ×100 before 51% reduction.) (B) Photomicrograph showing large, polygonal granular cell myoblastoma cells with fine eosinophilic granules and eccentrically placed nuclei. (Hematoxylin and eosin, ×400 before 51% reduction.)

origin. Subsequent ultrastructural and immunohistochemical studies of GCM also demonstrated their similarities to Schwann cells [8, 9], thus lending more support to their more recent nomenclature, granular cell schwannoma.

Granular cell myoblastomas of the bronchus are essentially benign neoplasms. However, both isolated malignant endobronchial GCM [10] and the coexistence of a benign GCM and a bronchogenic adenocarcinoma [11] or a squamous cell carcinoma [12] have been reported. As tracheobronchial GCM arises in the bronchi, its clinical manifestation is bronchial obstruction, and tissue diagnosis is made by bronchoscopic biopsy.

The gross appearance of the endobronchial GCM ranges from a several-millimeter ridgelike thickening of the mucosa to a sessile or pedunculated, polypoid lesion up to 6.5 cm in diameter [13]. The cut surface of the lesion is usually yellowish gray in color. Microscopically the typical GCM cell is large (200 to 300 μm in diameter) and polygonal, with strongly eosinophilic cytoplasm containing numerous prominent, deeply eosinophilic granules. The nucleus is small and eccentrically placed. The nucleoli are not prominent. Pseudoepitheliomatous hyperplasia of the overlying mucosa is quite frequent and occasionally causes some confusion in differentiating between squamous cell carcinoma and GCM. In about one third of the cases the lesion extends through the entire thickness of the bronchial wall into the parabronchial tissue [13]; however, involvement of the lung parenchyma is quite rare. There are no serum markers for GCM and diagnosis by exfoliative cytology is usually not feasible.

The preferred management of bronchial GCM is clearly surgical resection when there is evidence of extensive destruction of the lung parenchyma caused by chronic obstruction. Depending on the location of the lesion and the extent of parenchymal destruction, either lobectomy or, infrequently, pneumonectomy may be required. Occasionally computed tomographic scan of the tracheobronchial tree is helpful in preoperative decision making between lobectomy with sleeve resection and pneumonectomy when the main bronchus is involved [14]. Lesions occurring in the trachea can also be successfully managed by resection and reconstruction [15]. The appropriate management of a small, asymptomatic GCM has not been clearly established. Several recent articles advocated endoscopic removal (with or without use of a laser) of these lesions. However, the incidence of recurrence within 2 years after endoscopic removal has been reported to range from 10% to 54% [3, 6]. Because of the potential of GCM for rapid growth and bronchial obstruction, the high incidence of parabronchial tissue involvement rendering complete endoscopic removal unlikely, and the small but definite potential for malignant transformation, we feel that adequate surgical resection is the treatment of choice. After surgical excision, long disease-free intervals can be expected in 85% of the patients [16, 17]. Radiation therapy and chemotherapy have not been proven effective [13, 18].

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Treatment of Postoperative Chylothorax With Intrapleural Fibrin Glue

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Two patients with chylothorax after pulmonary resection for lung cancer were successfully treated without thoracotomy by injection of fibrin glue components into the pleural cavity. This new technique for closing the chylous leak is described.

(Ann Thorac Surg 1989;48:116–8)

Current aggressive surgical approaches for the treatment of lung cancer, which involve mediastinal lymph node dissection, may cause an increase in the incidence of chylothorax after resection for lung cancer. This report describes a new treatment of chylothorax after pulmonary resection with injection of fibrin glue components into the pleural cavity.

Patient 1

A 65-year-old woman underwent a right lower lobectomy with mediastinal lymph node dissection for adenocarcinoma of the lung. On the third postoperative day, after she began oral intake, pleural drainage increased and changed to a chylous effusion. Chemical analysis of the fluid revealed a high triglyceride and a low cholesterol content. All oral intake was stopped and intravenous hyperalimentation was begun. The pleural drainage gradually decreased but persisted at a rate of 700 to 800 mL/day. A chest roentgenogram showed the existence of a pleural dead space after the lobectomy (Fig 1).

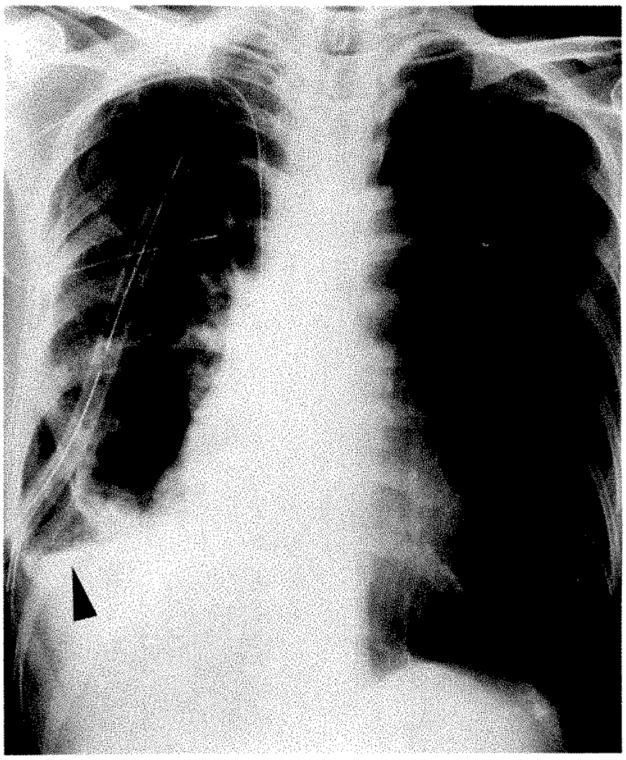

Fig 1. (Patient 1.) Chest roentgenogram on the third postoperative day. A pleural dead space and effusion (arrow) *are seen.*

On the seventh postoperative day, intrapleural fibrin gluing was performed for the purpose of sealing the leakage point. After the pleural effusion was drained, the patient was placed in the left lateral position and the fibrin glue components were introduced into the pleural space through the chest drainage tube. Under fluoroscopy, the tip of the tube was moved nearer to the lower mediastinum, where the fistula seemed to exist. First, 10 mL of concentrated fibrinogen solution (component A) was introduced with air insufflation. Next, 10 mL (10,000 units) of thrombin solution with 40 mmol/L calcium chloride and 3,000 KIU of aprotinin (component B) was instilled. After instillation, the pleural drainage decreased to a rate of 180 to 250 mL per day. Therefore, four days later, the chest tube was removed. A low-fat diet was continued for a week. Because only slight pleural effusion persisted, normal oral intake was permitted to begin on the 15th postoperative day, after which the patient experienced an almost normal, uneventful recovery.

Patient 2

A right upper lobectomy and extirpation of mediastinal lymph nodes were performed in another institution in a 65-year-old man for adenocarcinoma of the lung. On the second postoperative day, after oral intake was permitted, a chylothorax developed. Because the chylothorax did not respond to any form of conservative treatment, 5 weeks after the operation the patient was transferred to our hospital.

A lymphangiogram revealed that the chylous leakage occurred at the level of the lower part of the azygos vein and connected with the upper pleural space (Fig 2). Six weeks after the operation, fibrin gluing in the right upper pleural cavity was performed. After the pleural effusion

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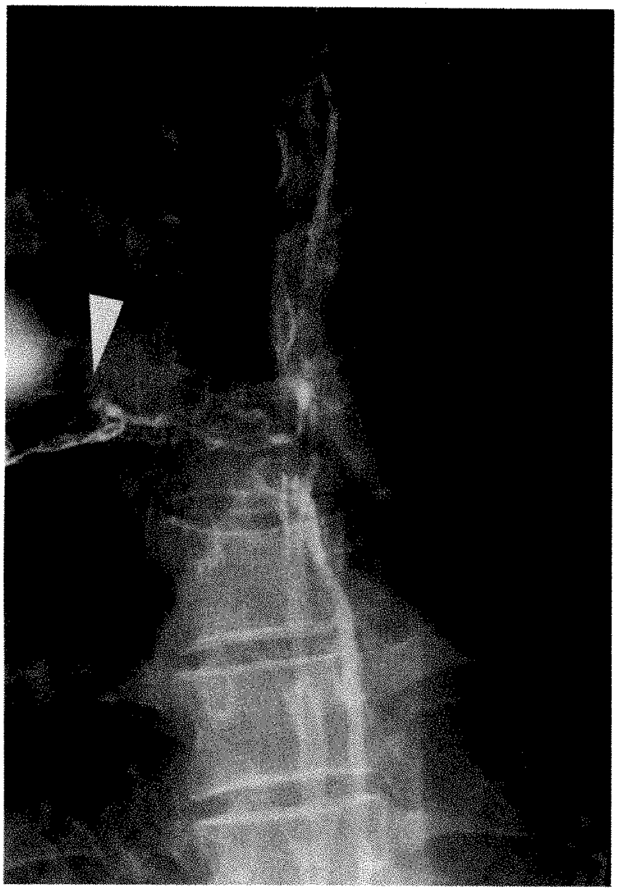

Fig 2. (Patient 2.) Lymphangiogram before gluing, showing chylous fistulas connected with pleural space (arrow).

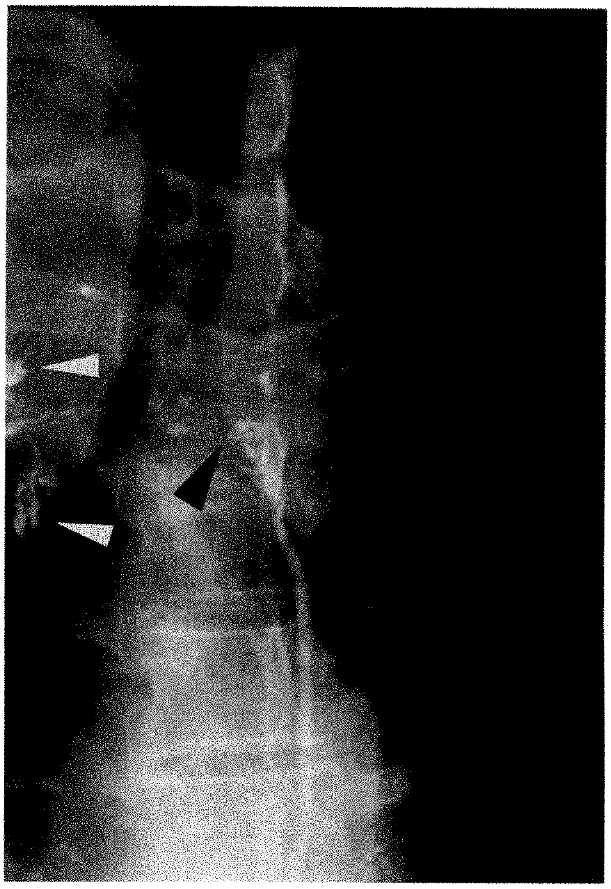

Fig 3. (Patient 2.) Lymphangiogram 1 month after gluing. A major fistula is blocked (black arrow). White arrows *mark contrast medium deposited in the lymph nodes after the first lymphangiography.*

was drained and the patient was placed in a suitable position, 20 mL of each component of fibrin glue was injected into the pleural cavity, first component A and then component B. From the next day, a medium-chain triglyceride diet and intermittent positive-pressure breathing were continued for a week, and the pleural effusion gradually decreased. Thereafter, normal oral intake was permitted, but the effusion did not increase. A lymphangiogram 4 weeks after the gluing showed that only a few fistulas of the thin lymphatic channels persisted, and the major fistula had closed (Fig 3). The patient experienced an uneventful recovery. Four months after the gluing, the chylothorax was completely absorbed.

Comment

Most cases of chylothorax after thoracic operations without pulmonary resection can be successfully treated with dietary management or pleural drainage, or a combination of the two. However, after pulmonary resection, especially pneumonectomy, because the chylous fistula often cannot be completely sealed by the lung due to remaining pleural dead space, the chylous leakage sometimes persists even with conservative forms of treatment. In such cases, if the actual point of leakage in the thoracic duct can be defined, direct ligation may be the most certain procedure for closing the leak [1]. Lymphangiography is useful for the identification of the leakage point, as reported by Heilman and Collins [2]. Because surgical closure of the leak is rather difficult, we first tried to conservatively apply fibrin glue for a closure of the persistent chylous leak, because the gluing was a very easy procedure and seemed to be almost as effective for closing the chylous leak as direct ligation of the thoracic duct. The safety of this technique with regard to hepatitis B and acquired immunodeficiency syndrome viral infection has been established [3], and now this glue is widely used for hemostasis and for closing any type of fistula in thoracic operations [4, 5].

In our method of gluing without thoracotomy, fibrinogen solution is introduced into the pleural cavity to cover part of the dissected mediastinum in a suitable position. After this, by an injection of thrombin solution, a fibrin seal can be formed on part of the mediastinum. With this application of the glue components, chylous fistulas can be closed successfully, as shown in Figure 3. In the case of a lobectomy, intermittent positive-pressure breathing is a very useful supportive procedure for this method.

In this application, a large quantity of glue components is required. However, we think that when the leakage point is identified clearly by lymphangiography, as in patient 2, a lesser dose of the glue components may be sufficient to seal the leakage point by direct application during thoracoscopy with a flexible fiberoptic bronchoscope [6].

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REVIEW OF RECENT BOOKS

Cardiothoracic Trauma
By Panagiotis N. Symbas
Philadelphia, W.B. Saunders, 1988
404 pp, illustrated, $89.00

Reviewed by F. William Blaisdell, MD

This comprehensive text on cardiothoracic trauma is written by one of the real experts in the field. The book is 404 pages and consists of 20 chapters and an excellent index. The subject matter covered includes initial general management and management of all of the various forms of cardiac trauma including tamponade, penetrating wounds, contusion, pericardial injuries, ruptures of the heart, and traumatic intracardiac injuries. There are also chapters on traumatic aneurysm of the heart, coronary artery injury and missiles in the heart, and pulmonary and systemic injuries.

One of the most outstanding chapters is that related to trauma of the great vessels including penetrating and blunt ruptures. Various techniques available to control the circulation during thoracic aortic occlusion are discussed, and the author's favorite method is presented in detail.

The chapter on lung injuries is somewhat disappointing. There is very little emphasis on the anatomy or on principles of lung resection when this type of treatment is indicated. The chapter on major airway injury is excellent as is the chapter on esophageal injuries. The chapter on the pleural space includes pneumothorax, hemothorax, posttraumatic empyema, and traumatic chylothorax. Unfortunately, there is no discussion of the specific causes of hemothorax or discussions of operative approach. Intrathoracic bleeding is most commonly from the chest wall, but it can be from the lung, and very importantly, can be secondary to intraabdominal injury. Methods of identifying or recognizing the latter are not discussed.

The final two chapters are on diaphragmatic injuries and chest wall injuries. One of the major advances in the management of patients with multiple rib fractures has been the use of epidural anesthesia. This is mentioned only in passing in the chapter on flail chest.

In summary, this is an excellent work and consistent in its approach as it is entirely the work of one author. It is an impressive work and a major contribution to the literature on trauma.

Sacramento, California

Detection of Multiple Cardiac Papillary Fibroelastomas Using Transesophageal Echocardiography

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Papillary fibroelastomas are rare, benign cardiac tumors that may be associated with embolization, angina, and sudden death. We report a case of multiple papillary fibroelastomas diagnosed during life by transesophageal echocardiography. Surgical resection during mitral valve replacement for rheumatic mitral stenosis prevented the development of any of the life-threatening complications sometimes associated with this tumor.

(Ann Thorac Surg 1989;48:119–21)

Primary cardiac neoplasms are rare tumors with an autopsy incidence ranging from 0.002% to 0.33% [1]. Approximately 80% of these tumors are benign, the most common being myxomas, lipomas, papillary fibroelastomas, and hemangiomas. Papillary fibroelastomas are the third most common type, yet no more than 100 cases have been reported [2, 3]. The vast majority of these cases were incidental autopsy findings. On rare occasions, these tumors have resulted in transient ischemic attacks, stroke, angina, and sudden death [2, 4]. To our knowledge, only 11 cases of papillary fibroelastoma have been diagnosed during life, either preoperatively using echocardiography or intraoperatively [2, 4–6]. We describe a case of multiple papillary fibroelastomas seen on transesophageal echocardiography during life.

A 48-year-old woman was referred to the Los Angeles County Harbor/UCLA Medical Center for mitral valve replacement because of rheumatic mitral stenosis. Over the previous 4 months she had noted increasing shortness of breath, dyspnea on exertion, pedal edema, and nocturia. The patient had undergone mitral valve commissurotomy 20 years previously in Mexico for mitral stenosis due to rheumatic heart disease. Vital signs were normal and physical examination revealed an irregularly irregular heart rate and a grade 2/6 diastolic rumble at the apex. Results of a neurological examination were normal. Results of laboratory studies were normal, and a chest roentgenogram revealed left atrial enlargement. Electrocardiogram showed atrial fibrillation with a ventricular rate of 72 beats per minute. Angiography revealed a calcification in the mitral valve, mitral stenosis, moderate to severe mitral regurgitation, normal coronary arteries, and multiple radiolucent areas in the left ventricular outflow tract consistent with tumor versus thrombus or vegetations. Standard transthoracic and transesophageal echocardiography were performed and revealed marked left atrial enlargement, thickening of the mitral valve leaflets, 3+ mitral regurgitation, and a mitral valve area of 1 cm^2. Multiple 1-cm masses were seen on the mitral valve and in the left ventricle near the left ventricular outflow tract and along the septum. Transthoracic two-dimensional echocardiography was unable to identify the point of attachment of the masses, so that differentiation of the masses from multiple thrombi or vegetations was not possible (Fig 1). Transesophageal echocardiography, on the other hand, clearly demonstrated that the masses were pleomorphic, mobile, and attached by a short pedicle to the left ventricular and valvular endothelium (Fig 2).

At operation, ten round, soft masses measuring 0.5 to 1 cm in diameter were found. Five tumors were situated on

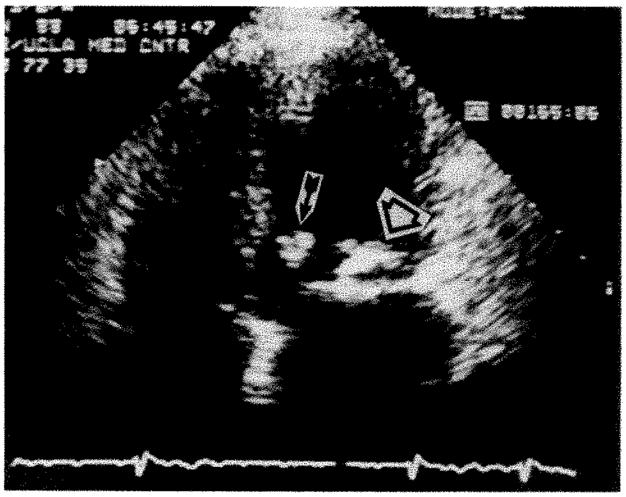

Fig 1. Apical four-chamber two-dimensional echocardiogram. The thickened mitral valve is seen (clear arrow)*. A mass in the left ventricular outflow tract is apparent, but its site of attachment is unclear* (solid arrow)*. It is also uncertain whether the mitral valve thickening is only due to rheumatic disease or represents additional masses on the ventricular side of the valve.*

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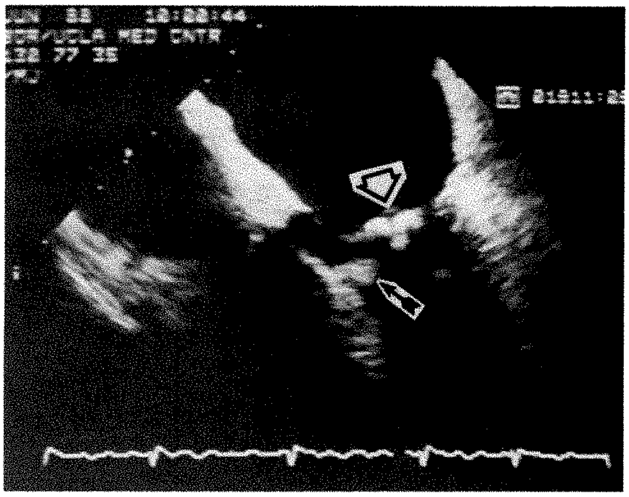


Fig 2. Transesophageal two-dimensional echocardiogram. The pedicle attaching the mass in the left ventricular outflow tract to the ventricular septum is clear (solid arrow)*. Multiple small nodules on the mitral valve are also apparent* (clear arrow)*.*

the subvalvular apparatus of the mitral valve and five were seen in the left ventricle along the septum and at the apex. The masses were all removed using simple surgical excision. Frozen section revealed benign papillary fibroelastoma. The rheumatic mitral valve was excised and replaced with a 31-mm St. Jude prosthesis. The patient's postoperative course was unremarkable, and she was discharged after adequate anticoagulation with Coumadin (crystalline warfarin sodium; Du Pont Pharmaceuticals, Wilmington, DE).

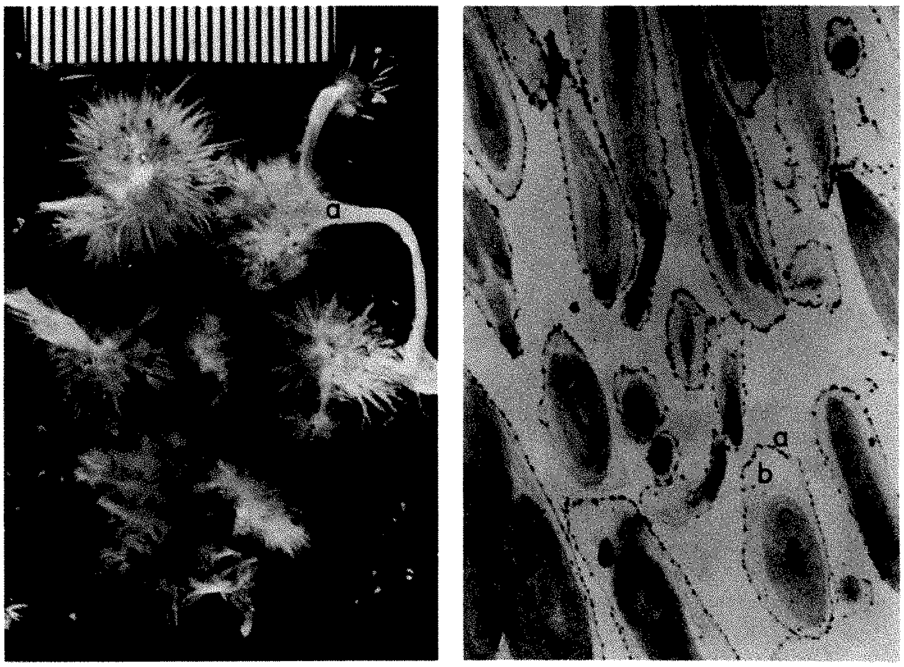
Comment

Cardiac papillary fibroelastomas are rare benign tumors, usually discovered as incidental findings. Although generally asymptomatic, these lesions have been known to cause stroke, transient ischemic attacks, angina, and sudden death. Four patients with papillary fibroelastomas and neurological symptoms have been described with symptoms including expressive aphasia, transient hemiparesis, and monocular blindness [2, 4]. In 6 other patients, angina or sudden death was attributed to aortic valve papillary fibroelastomas [2]. Postmortem examinations in those cases demonstrated that the tumors caused either obstruction or ball valve occlusion of a coronary ostium.

On gross examination these tumors have been described as resembling sea anemones (Fig 3A), with multiple papillary fronds attached to the endocardium by a short stalk [3]. They are usually single and less than 1 cm in diameter, and most frequently arise from the valvular endocardium [4]. However, they have been found on all cardiac valves and in all cardiac chambers. In the largest reported autopsy series, the majority of the tumors were on the aortic valve. Only one tumor was found in the left ventricle, and in only 3 of the 42 cases were the tumors multiple in number [3]. Interestingly, in our patient, there were ten tumors and five were situated in the left ventricle. Histologically, the tumor consists of delicate fingerlike projections composed of cores of dense fibrous tissue containing laminations of concentrically arranged elastic fibers [7]. The cores are surrounded by a loose acid mucopolysaccharide matrix containing scattered smooth muscle cells (Fig 3B).

The diagnosis of papillary fibroelastoma is usually made at postmortem examination. With the increased use of transthoracic two-dimensional echocardiography, these lesions have been discovered preoperatively. Our case represents the 12th case diagnosed during life and perhaps the first case of multiple papillary fibroelastomas seen using transesophageal echocardiography. Trans-

Fig 3. (A) Papillary fibroelastomas suspended in saline, showing the classic resemblance to sea anemones. Note attachment of stalk to a chorda tendinea (a)*. (B) Microscopic appearance of delicate, fingerlike projections. The endothelial cell lining* (a)*, mucopolysaccharide matrix containing smooth muscle cells, fibroblasts, and collagen fibrils* (b)*, and dense collagenous core with elastic fiber laminations* (c) *are demonstrated. (Hematoxylin and eosin, ×400 before 23% reduction.)*



A

B

esophageal echocardiography has been used for intraoperative monitoring of left ventricular contractility, detection of intracardiac air, and intraoperative assessment of mitral valve function [8]. Transesophageal echocardiography has been used to visualize cysts in a left atrial myxoma that could not be seen using standard two-dimensional echocardiography [9]. Although angiography and standard transthoracic two-dimensional echocardiography demonstrated in our patient the presence of multiple masses, their morphology and insertion could not be ascertained. Transesophageal echocardiography provided superior images of the tumors, including their pleiomorphism and their endocardial attachment by short pedicles. This better image is due to transesophageal echocardiography's superior resolution and the lack of intervening structures.

Because of the potential for embolization, angina, and sudden death, the recommended treatment for papillary fibroelastomas is surgical resection. This is particularly true for tumors located near the coronary ostia, where the risk of angina and sudden death is increased. Although transesophageal echocardiography provides excellent resolution, neither transesophageal echocardiography nor standard two-dimensional echocardiography can reliably distinguish papillary fibroelastomas from other cardiac lesions such as myxomas, mural thrombus, vegetations, or other cardiac neoplasms. This further supports the recommendation of elective surgical resection. Simple surgical excision with valvular repair is the recommended approach if the tumor is situated on a valve [4].

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Treatment of Median Sternotomy Wound Infection and Sternal Necrosis in an Infant

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A case of an infant with median sternotomy wound infection and sternal necrosis treated by debridement and muscle flap transposition is reported. As in adults, the procedure can be done safely and successfully. Rapid healing and chest wall stability were obtained. A later cardiac procedure was performed without technical difficulties and without untoward effects on chest wall stability.

(Ann Thorac Surg 1989;48:122–3)

Median sternotomy has become the standard approach in both children and adults for cardiac and mediastinal procedures. Infection and subsequent sternal dehiscence is an extremely serious complication and ranges in incidence from 0.8% to 1% in recent adult series [1, 2]. This complication is thought to be extremely unusual in children and reports are few. We recently treated a 6-week-old infant who developed a deep sternotomy wound infection and sternal necrosis after pulmonary artery banding by using muscle flaps as previously described in adults [3, 4]. The infant recovered and subsequently has undergone successful closure of the ventricular septal defect and removal of the pulmonary artery band through a repeat midline "sternotomy incision."

A 1-month-old, severely malnourished 2.0-kg infant with severe heart failure and failure to thrive because of a large ventricular septal defect underwent pulmonary artery banding via median sternotomy. Despite initial improvement, it was believed that the band was too loose and it was subsequently revised. This second procedure was complicated by staphylococcal infection and wound dehiscence. At exploration, both sternal halves, including manubrium, were noted to be necrotic and were debrided. Marked paradoxical chest wall motion was noted with inspiration. After two operative debridements (Fig 1), closure was obtained by transposing the right pectoralis major, pedicled on its thoracoacromial blood supply, into the upper half of the defect and the right rectus abdominis based on the internal mammary (superior epigastric) artery into the lower half of the defect. A split-thickness skin graft was applied to the uncovered muscle. Operative blood loss was limited to 50 mL by careful bipolar electrocautery. The patient healed uneventfully. Paradoxical chest wall motion decreased steadily as the reconstruction "stiffened" and was unnoticeable by 6 weeks postoperatively. By 9 months postoperatively (Fig 2), muscle flaps and skin graft had hardened considerably.

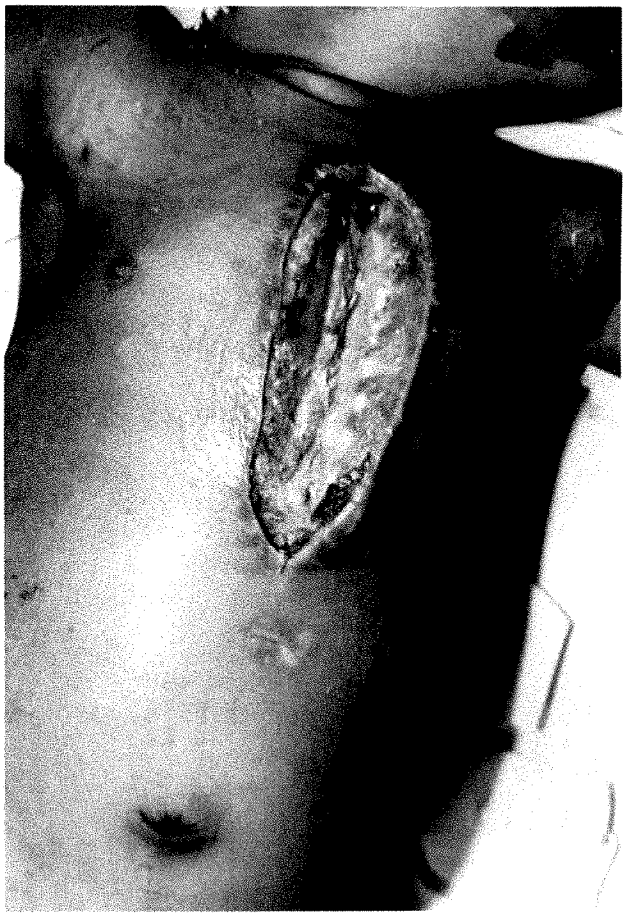

Fig 1. Clean, open mediastinal wound. Necrotic sternum has been debrided; note ends of costal cartilages in left wound margin.

In September 1987, the patient underwent removal of the pulmonary artery band and ventricular septal defect repair. A median approach through the muscle flaps was performed. A thick layer of fibrocartilaginous tissue was encountered from beneath which pericardium and ventricular wall were easily separated. The operative procedure was uncomplicated. The wound healed uneventfully, and the chest wall was again stable. The child has subsequently grown normally and continues to do well.

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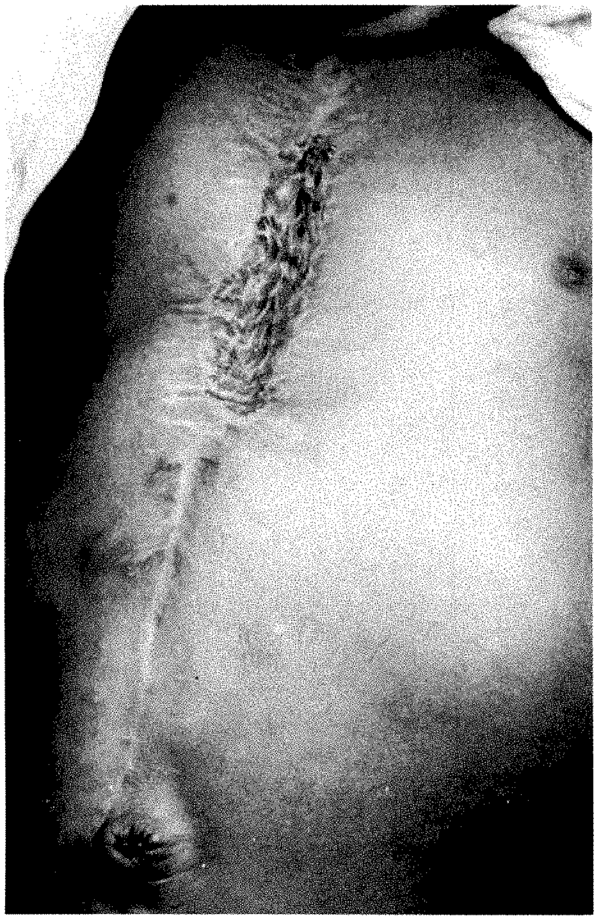

Fig 2. Chest wall healed and stable at 9 months of age.

Comment

To our knowledge, our patient is the youngest reported to date with this complication and the only one of the reported cases in the age group to be treated by muscle flap coverage and subsequently reoperated on [5]. Coverage of the debrided defect with pedicled muscle flaps has been well documented in adults [3, 4, 6, 7]. Advantages include the ability to obliterate dead space and to decrease residual bacterial load with well-vascularized tissue. In addition, it has been noted in adults that, despite muscle atrophy, the resulting fibrotic bridge spanning the sternal defect stabilizes the anterior chest wall sufficiently and prevents serious paradoxical motion and ventilatory insufficiency. Disadvantages include the loss of donor muscle function and possible ventral hernia formation with use of the rectus abdominis. In a child this young might also be included the difficulty of dissecting such thin structures and small pedicles, substantial operative blood loss, and theoretical effects on future chest wall growth.

In this particular patient, with such an extensive infection and with the sternum necrotic, there was, in effect, no other good option. Although omentum has been used in adults [7], its likely small volume in this age group, the necessity of a laparotomy to obtain it, and desire for chest wall rigidity all mitigate against its use as a primary treatment option. Though the structures are quite small, expeditious dissection was facilitated by loupe magnification. Blood loss was limited by assiduous hemostasis. At 1 year postoperatively the chest wall is rigid and stable; there is no evidence of abdominal wall hernia or diastasis. There is no asymmetry of anterior ribs, but chest wall growth is far from complete in this patient.

The cardiothoracic surgeon is often concerned about the difficulties of reentering the mediastinum in any of the patients who survive this complication and heal the chest wound. This is particularly the case in the infant population, as repeat procedures are common. Can the heart and great vessels be easily and safely isolated from the midline muscle and scar tissue? Will the chest wall be stable after repeat sternotomy? In this patient, the incision was made through the middle of both flaps. Between the flaps and the heart itself was an easily developed plane allowing safe and surprisingly rapid exposure of the right ventricle and pulmonary artery. Postoperatively the chest wall was stable; the incision healed uneventfully. The technique of muscle flap transposition may be applied in infants as in adults to manage severe median sternotomy wound infection.

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Autopsy Findings 14 Years After Septation for Single Ventricle

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The autopsy findings of a patient who survived 14 years after ventricular septation for single ventricle are reported. Although the patient had been well for years, she suddenly died at 22 years of age. Her ventricular free walls had grown normally, but the ventricular septum did not. A crevice was found in the apex, and the ventricular septum consisted of only the Teflon patch. Microscopically, fibrosis was found only in the right atrium.

(Ann Thorac Surg 1989;48:124–5)

As corrective surgery for single ventricle, ventricular septation [1, 2], modified Fontan operation [3], and, in some particular cases, total cavopulmonary shunt operation [4] have been utilized. Since 1970 ventricular septation has been performed in 16 patients with single ventricle in our institution. The longest survivor, who was operated on in 1970, suddenly died after 14 years' active life. This report documents the autopsy findings of the case.

The patient had originally complained of severe cyanosis and squatting. Hemodynamic investigation and angiocardiogram were performed at 8 years of age, and revealed interventricular right-to-left shunt and no atrioventricular valve regurgitation. A corrective operation was undertaken [2]. When the infundibular muscle was removed through the right ventriculotomy no interventricular septum was found except a large muscle bundle in the bottom of the ventricle. Both atrial chambers connected to a sole ventricular chamber in the usual fashion (situs solitus). The trabeculae revealed neither right nor left ventricular characteristics. No rudimentary chamber was found. There were two intact atrioventricular valves, and the great arteries were normally related. Undivided ventricle instead of single left ventricle seemed to be a more suitable diagnosis for this case from the pathological knowledge the surgeon (Y.K.) had at the time of this operation. As a diagnosis of single ventricle {I,C,S} by the classification system of Van Praagh and associates [5] with infundibular pulmonary stenosis was confirmed, ventricular septation was performed with a Teflon patch, 25 × 35 mm in size, of which the lower margin was sutured onto the ventricular muscle bundle. The slit between the bundle and the ventricular wall was closed with three interrupted sutures. The right ventricular outflow tract was reconstructed using a Teflon patch lined with pericardium.

The patient's postoperative course was uneventful. At discharge from the hospital, electrocardiography revealed sinus rhythm with incomplete left bundle-branch block. She was asymptomatic and lived a normal life until 20 years of age. No heart murmur was detected. Postoperative cardiac catheterization, angiocardiography, and ultrasonic cardiography were performed 3 and 7 years after the corrective operation. The results showed excellent hemodynamics and cardiac function [6, 7].

The patient was admitted to our hospital with an episode of tachycardia when she was 20 years of age. Electrocardiography showed atrial flutter that was converted to sinus rhythm by direct current shock. Only unifocal ventricular ectopic beats were sporadically found in an ambulatory electrocardiogram after the recovery. The cardiothoracic ratio was 55%. Ultrasonic cardiography revealed no particular change except slight paradoxical movement of the created interventricular septum [7]. She was discharged with regular sinus rhythm. Although there were four episodes of tachyarrhythmia during the last 2 years of her life, she had been doing well while she was in normal sinus rhythm. When she was 22 years old, she suddenly collapsed and was urgently admitted to a nearby hospital, where she was pronounced dead.

The autopsy findings were the following. The heart weighed 420 g and had a normal ventricular wall thickness, 9 mm in the right and 15 mm in the left-sided ventricle created by the septation (Fig 1). The volume of both ventricles was satisfactory given her physical constitution. The interventricular septum, however, was almost entirely composed of the Teflon patch covered with a thin layer of fibrous tissue, through which the suture materials were seen. Crevice formation 2 cm in depth was found in the apex between the right and the left ventricle (see Fig 1). No stenosis was found in the right ventricular outflow tract. The atrioventricular valves and the distribution of the coronary artery system looked normal.

Microscopically, there was no abnormal finding in the myocardium of both ventricles. In the free wall of the right atrium, however, extensive severe fibrosis was found.

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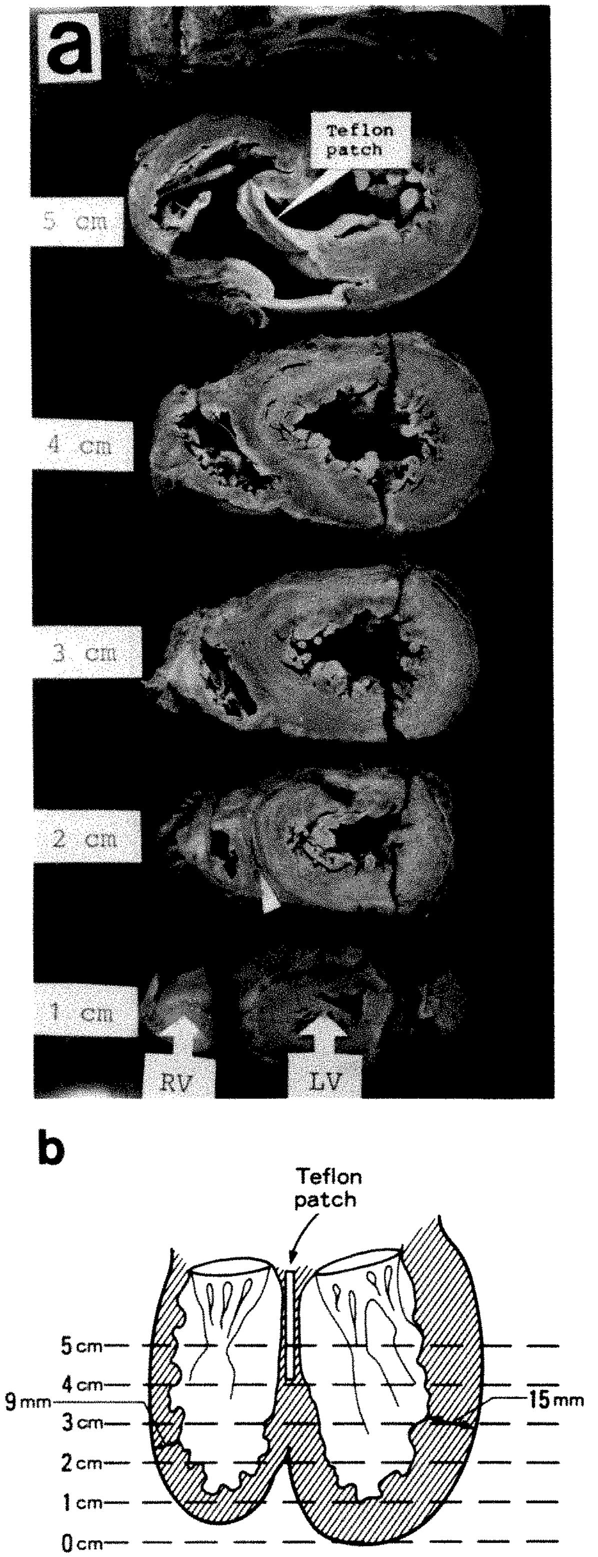

Fig 1. Cross section of the heart 14 years after septation for single ventricle. (a) Photograph of the cross sections sliced in 1 cm thickness from the apex of the left ventricle. (b) Schema of slicing lines. A crevice, 2 cm in depth, was found in the apex between the left and right ventricle.

Comment

One of our interests concerning ventricular septation for single ventricle performed during childhood is that of growth of the heart. This report documents the autopsy findings in a 14-year survivor with single ventricle who underwent ventricular septation at 8 years of age. The patient, although she had several episodes of atrial flutter during the last 2 years of her life, led a full and active life for more than 12 years after the corrective operation, and suddenly died at 22 years of age from unknown cause.

The autopsy findings suggest that the reconstructed heart with a prosthetic septum had grown up well with morphologically normal myocardial architecture of the ventricular wall. Both ventricles developed satisfactorily in volume and in wall thickness suitable to each ventricular function. The interventricular septum, however, did not develop well, and was almost entirely composed of the Teflon patch. Crevice formation found in the apex seemed to result from the nongrowing septum. In a report of postoperative study of patients with ventricular septation, Shimazaki and co-workers [6] hypothesized that the size of the prosthetic septum should be as small as possible because the paradoxical movement of the noncontractile area could impair left ventricular function. It seemed that the nongrowing small septum, which was confirmed to be almost entirely composed of the small Teflon patch, did not affect the patient's cardiac function throughout her life.

Extensive replacement of the right atrial myocardium by fibrosis may presumably relate to the atrial flutter, but it is not certain that the fibrosis caused ultimately fatal arrhythmias, which could not be predicted by Holter electrocardiography.

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Primary Neurilemoma of the Diaphragm

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A neurilemoma of the diaphragm in an asymptomatic 46-year-old woman is reported, and 12 cases of primary neural tumor of the diaphragm reported previously are reviewed. The common symptoms in these patients are chest pain, cough, and dyspnea. Joint pain or clubbing of the fingers is present in nearly half of the patients. As with diaphragmatic tumors in general, many neural tumors of the diaphragm are malignant. We believe that all such tumors should be resected through a thoracotomy incision, which affords optimal exposure of the diaphragm.

(Ann Thorac Surg 1989;48:126–8)

Primary neural tumors of the diaphragm are rare, representing approximately 10% of neoplasms of the diaphragm. Since the first report of a primary neurogenic diaphragmatic tumor in 1945 [1], only 12 such cases have been recorded. This study reports a patient with a neurilemoma of the diaphragm, and reviews previously reported cases of neural tumors of the diaphragm.

In September 1984, an asymptomatic 46-year-old woman was evaluated because of a mass in the right side of the chest seen on a roentgenogram (Fig 1). The mass had been seen on a chest roentgenogram 5 years earlier, and at that time was thought to represent a cyst or diaphragmatic hernia. The mass appeared to have increased in size during the 5 years. The patient did not smoke. Her medical history included a cardiac arrest 8 years earlier, which was thought to have resulted from an overdosage of "diet pills" and thyroid medication. She was subsequently thought to have forgetfulness and impaired ability to concentrate. Her physical examination was normal.

The chest was explored through the right fifth intercostal space. A multilobulated, firm, 10-cm mass was found attached to the right side of the diaphragm. A biopsy was performed, and the tumor was found to be composed primarily of spindle cells. Because of concern that the tumor might arise from or involve the liver and because of poor exposure of the posterior and inferior aspects of the tumor, the operation was stopped. During the next several days, the patient was evaluated with a liver scan and computed tomography (Fig 2), both of which showed that the tumor did not involve the liver.

Five days after the first operation, the tumor (Fig 3) was completely removed by means of a thoracotomy through the bed of the resected 11th rib. The diaphragmatic defect was closed primarily. Recovery was uneventful. Histological examination revealed that the tumor was composed of interdigitating bundles of spindle cells. Focally, evidence of palisading nuclei was seen. The microscopic features were those of a neurilemoma. The patient has been followed for 4 years without evidence of recurrence.

Comment

Primary tumor of the diaphragm was first reported in 1868 when Grancher [2] discovered a fibroma of the diaphragm during an autopsy. The most exhaustive review of the subject, by Wiener and Chou [3] in 1965, documented 71 diaphragmatic tumors. An additional 14 cases were reviewed by Olafsson and associates [4] in 1971. Of these 85 total cases, 52 (61%) were benign, including 18 cystic tumors. Thirty-three (39%) of the tumors were malignant.

Diaphragmatic tumors can be seen at any age, but more than half of the patients are between 40 and 60 years old. Men and women are affected equally. According to Wiener and Chou [3], 80% of patients are symptomatic, with chest or abdominal pain, cough, and dyspnea being the most common complaints. Twenty percent of patients are asymptomatic; in these patients, the tumors were discovered incidentally on routine chest roentgenogram or at autopsy.

Including the present case, 13 cases of primary neural tumors of the diaphragm have been reported, including 4 neurilemomas, 6 neurofibromas, and 3 neurofibrosarcomas (Table 1). Nine patients were female and 4 were male; their ages ranged from 5 to 65 years. These tumors involved the right side of the diaphragm in 6 patients and the left side in 7.

Nine of the 13 patients were symptomatic, with cough, chest pain, dyspnea, and clubbing of the fingers being the most common complaints. Three patients, including the one described here, were asymptomatic. Six patients with primary neural diaphragmatic tumors had clubbing of the fingers. In fact, in 2 of the 6 patients, clubbing was the only complaint. Wiener and Chou [3] found that clubbing of the fingers was associated almost exclusively with neural tumors of the diaphragm. Clubbing of the fingers was seen in more than 60% (5/8) of the neural diaphragmatic tumors, but was seen in only one of the remaining 63 diaphragmatic tumors that were not of neural origin.

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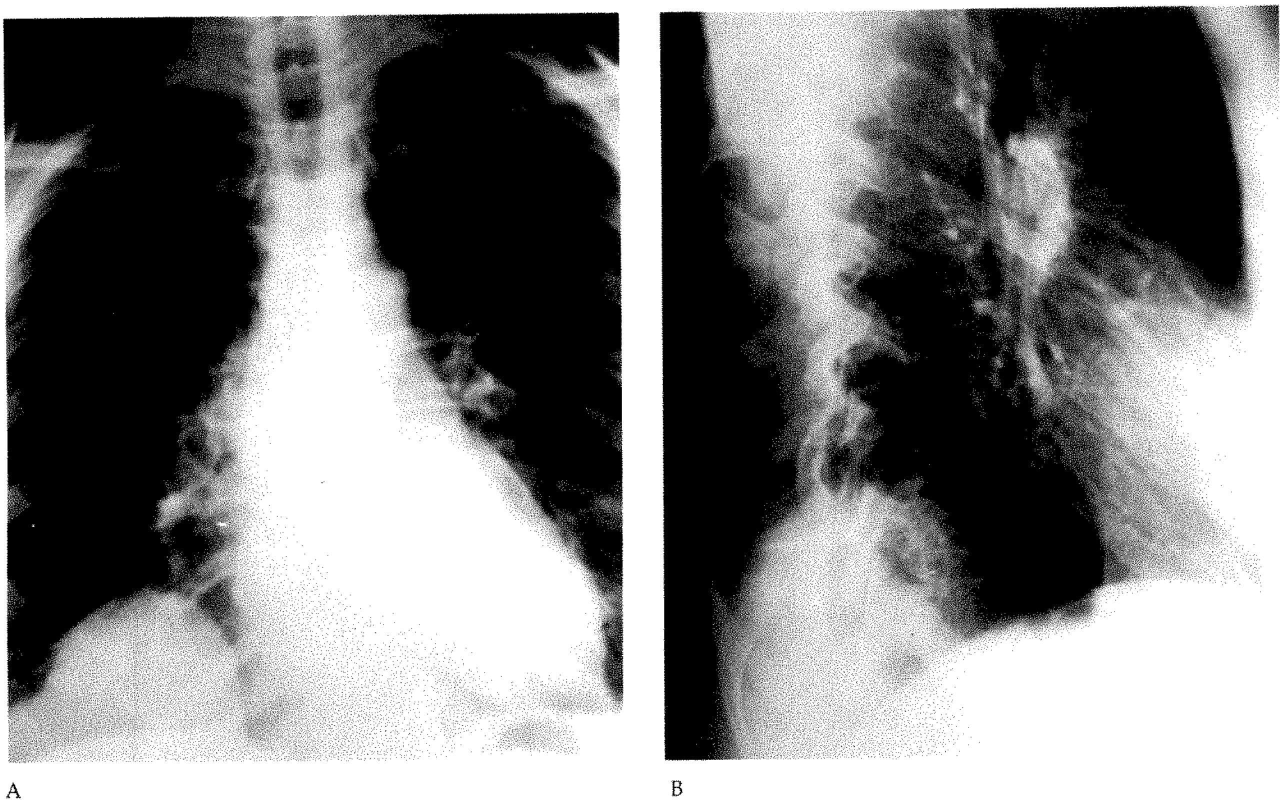

Fig 1. Mass in right side of chest seen on (A) posteroanterior and (B) lateral chest roentgenograms.

Surgical removal of the tumor was uniformly successful in relieving the clubbing.

In addition to the standard chest roentgenogram, the preoperative evaluation of these tumors may be augmented by a liver-spleen scan, pneumoperitoneography, or computed tomography of the abdomen and chest. In

Table 1. Summary of Reported Cases of Neural Diaphragmatic Tumors

				Symptoms				
Author	Age	Sex	Side	Pain	Cough	Dyspnea	Joint Swelling or Clubbing	Pathological Diagnosis
Klassen et al [1]	42	M	R	+	+	−	+	Neurofibroma
Samson and Childress [5]	56	M	L	+	+	+	+	Neurofibrosarcoma
Samson and Childress [5]	50	F	R	+	−	+	−	Neurofibrosarcoma
Sweet and Gephart [6]	26	F	L	−	−	−	−	Neurofibroma
Weisel et al [7]	55	F	L	+	+	+	−	Neurilemoma
Trivedi [8]	5	F	L	−	−	−	+	Neurilemoma
Alix and Oliva [9]	57	M	R	−	−	−	+	Neurofibroma
Petrovskii and Nikolaev [10]	40	F	R	+	+	+	+	Neurofibroma
Sarot et al [11]	65	M	L	−	−	−	−	Neurilemoma
Kibardina [12]	56	F	L	+	+	+	−	Neurofibroma
Rabkin and Akperbekov [13]	40	F	R	ND	ND	ND	ND	Neurofibroma
Doyle [14]	37	F	L	+	−	−	+	Neurofibrosarcoma
McClenathan and Okada (present case)	46	F	R	−	−	−	−	Neurilemoma

F = female; L = left; M = male; ND = no data; R = right; + = present; − = absent

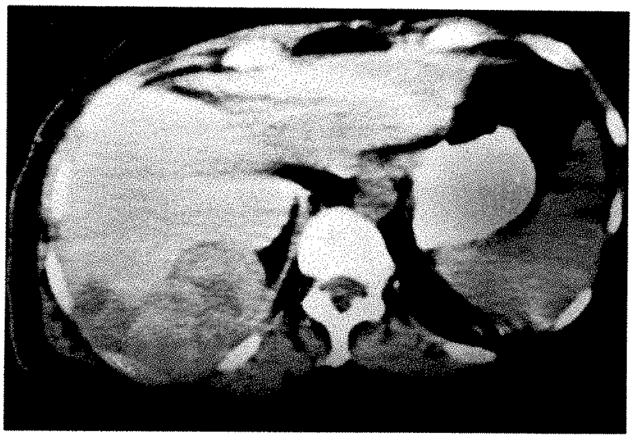

Fig 2. Computed tomographic scan shows mass.

our patient, the liver scan and tomographic scan were valuable in ensuring that the tumor did not involve the liver.

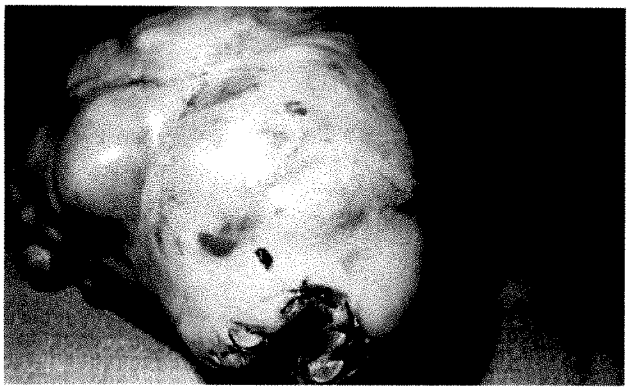

Fig 3. Gross morphological appearance of neurilemoma.

The appropriate treatment of primary neural tumors of the diaphragm is prompt surgical resection. The tumors should be approached through a thoracotomy incision, which will provide optimal exposure of the involved diaphragm.

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Use of a Double-Lumen Pressure Monitoring Catheter to Facilitate Pulmonary Artery Banding

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Pulmonary artery banding is facilitated by simultaneously measuring the pressure above and below the band. This can be accomplished with a commercially available double-lumen central venous pressure monitoring catheter. This catheter is inserted through the outflow tract of the right ventricle and positioned so that the band will be between the two lumens. Gradual tightening of the band can be accomplished while monitoring the pressures proximal and distal to the band.

(Ann Thorac Surg 1989;48:129)

Banding of the pulmonary artery is an accepted palliative technique in patients with excess pulmonary blood flow. Banding techniques vary somewhat from institution to institution, but adhere to the principle of reducing the pulmonary artery pressure distal to the band.

Many variables are used to assess the effectiveness of the banding. These include changes in heart rate, arterial oxygen saturation, the pressure gradient across the band, and the difference between the systemic pressure and the pulmonary artery pressure distal to the band. Trusler and Mustard suggested a technique that involves banding to a circumference based on the lesion added to the weight of the child, which has been critically evaluated long-term by Albus and associates [1].

A simple adaptation of a double-lumen central venous pressure catheter (Arrow International Inc, Reading, PA) so that the proximal and distal ports are connected to pressure transducers allows continuous monitoring of proximal and distal pulmonary artery pressures during the dynamic phase of the banding. These pressure changes are simultaneously compared with the systemic arterial pressure and correlated with arterial saturation and pulse rate.

Technique

A double-lumen central venous pressure catheter has both ports connected to pressure transducers. The thoracotomy is performed and a loose band is placed around the pulmonary artery. The catheter is then inserted through a small pursestring suture in the pulmonary artery or right ventricular outflow tract. The proximal and distal ports are approximately 2 cm apart, which facilitates positioning the two ports above and below the area to be banded. As the band is gradually tightened the pressures are continuously monitored and the changes in the two pulmonary pressures are observed. When adequate measurements are achieved the band is fixed in place. The chest retractor can be closed and the lung allowed to reexpand for more accurate assessment of the pressure dynamics. With completion of the procedure the catheter is removed and the pursestring suture tied. The chest is closed in the usual fashion.

Comment

Pulmonary artery banding is a standard procedure used in patients who cannot otherwise undergo definitive types of repair. Though it is our policy to perform early total correction, certain congenital lesions can only be palliated until a second-stage repair can be performed. In addition, many centers outside the US are not able to perform definitive operations on infants and the only option is palliation. The purpose in banding is to reduce pulmonary blood flow and protect the pulmonary arteries from hypertensive changes. Typically, measurements of pressures proximal and distal to the pulmonary band are compared with the systemic arterial pressure. A simple technique of using a double-lumen central venous catheter for simultaneous measurement of the pressures above and below the band is described. Utilizing the simultaneous pressure technique with the indwelling double-lumen catheter, it allows a more accurate estimation of the tightness of the pulmonary band. The band's effectiveness can be correlated with other variables such as arterial saturation, heart rate, and systemic pressure. This technique facilitates the pulmonary banding and eliminates the need for multiple pulmonary arterial sticks while allowing simultaneous monitoring of pressures. This technique has been used in 5 patients (newborn to 9 years of age) without complication.

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Heart/Heart-Lung Transplantation
The Domino Procedure

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Orthotopic heart transplantation has become an accepted therapeutic modality limited only by availability of donor organs. Heart-lung transplantation is also being performed with increasing frequency due to improvements in distant procurement techniques. Although the majority of patients requiring heart-lung transplantation have cardiac dysfunction, there is a subset with no cardiac compromise that can serve as donors of cardiac allografts before heart-lung transplantation. We report a technique for sequential heart/heart-lung transplantation in such a subset of patients.

(Ann Thorac Surg 1989;48:130–3)

Orthotopic heart transplantation has become a commonly performed treatment for patients with end-stage heart disease, although availability of suitable donor organs continues to limit its application. Heart-lung transplantation, initially less successful due to difficulties in lung preservation, is now being performed in increasing numbers, particularly with the introduction of simple hypothermic flush techniques that have allowed for distant procurement of heart-lung allografts. The majority of patients requiring heart-lung transplantation have severe cardiac dysfunction secondary to long-standing pulmonary disease. A substantial subset of patients with end-stage lung disease have no cardiac compromise. It has been suggested that such patients could serve as donors of cardiac allografts before heart-lung transplantation (personal communication from N. C. Cavarocchi to J. Wallwork at Papworth Hospital, Cambridge, England, October 1985). We present our clinical results with this technique for sequential heart/heart-lung transplantation in such a subset of patients.

Technique

Heart-Lung Donor Operation

After median sternotomy and removal of the thymus gland, the innominate vein is mobilized to its junction with the superior vena cava (SVC) and the azygous vein is identified and ligated. The aorta is dissected free from the pulmonary artery (PA) up to the level of the ligamentum arteriosum, and the innominate artery is encircled, ligated, and divided. The lateral pericardial reflection over the PA is mobilized and the innominate vein is ligated and divided. The pleurae are opened bilaterally and the inferior pulmonary ligaments mobilized. A pursestring suture is placed in the PA for placement of a pulmonary infusion catheter.

The pleurae are incised vertically through the phrenic nerves to the level of the hilum bilaterally. The PA is cannulated and a precooling infusion begun. The trachea is then dissected 5 cm above the carina.

The SVC is divided, the inferior vena cava (IVC) is clamped, and the heart is allowed to beat empty. The aorta is cross-clamped and the heart is arrested with 1 L of St. Thomas' solution at 4°C. The left side of the heart is decompressed by excising the tip of the left atrial appendage. Preservation of the lungs is accomplished using a hypothermic crystalloid flush technique [1]. After infusion of 300 mL of heart cardioplegia, gravity infusion of the pulmonary "plegia" solution is begun. After complete perfusion of both the heart and pulmonary circuit the aorta is transected, and the endotracheal tube is withdrawn to the level of the vocal cords. The lungs are inflated with room air to "half-volume" (10 mm Hg inflation pressure) and the trachea is clamped and divided. The posterior mediastinal dissection is initiated from the transected trachea, moving inferiorly behind the hila and anterior to the esophagus. An incision is made transversely across the inferior posterior mediastinum at the diaphragm and the dissection is completed. The heart-lung block is removed after ligation of the IVC.

Heart-Lung Recipient Operation

After standard median sternotomy, both pleural cavities are explored and any adhesions are taken down with electrocautery before heparinization. The pericardium is then incised anteriorly in the midline. Venous cannulation of the heart-lung recipient can be via the IVC as inferiorly as possible inside the pericardium or via the femoral vein (Fig 1). The SVC is cannulated above the SVC–right atrial junction and the azygous vein is controlled. An aortic cannula is placed in standard fashion in the ascending aorta, cardiopulmonary bypass is initiated, and the patient is cooled to 20°C. The aorta is cross-clamped and St. Thomas' cardioplegia is administered with decompression of the heart via an incision in the left inferior pulmonary vein. After administration of cardioplegia the heart is excised by dividing both the ascending aorta and the PA in their midportions, to allow adequate length for all subsequent anastomoses. The SVC

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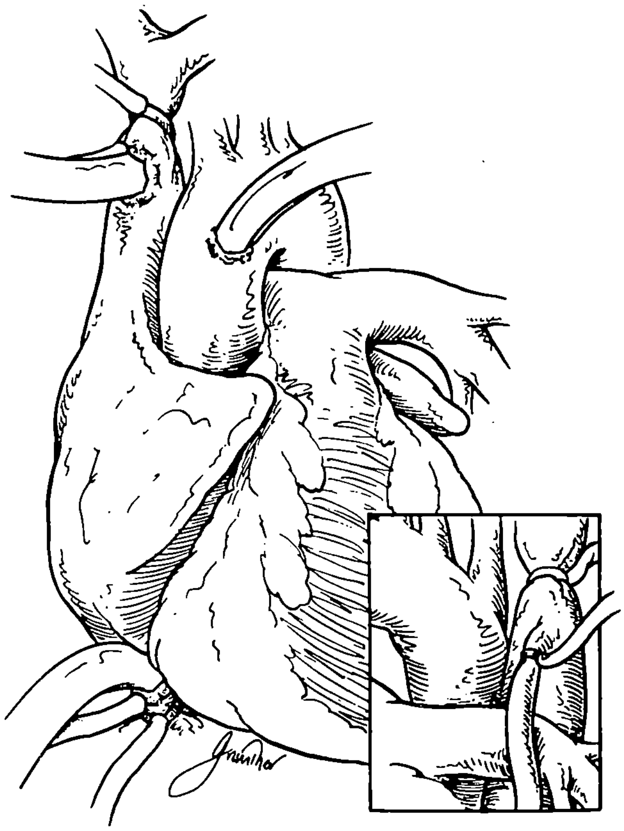

Fig 1. Venous cannulation of the heart-lung recipient. The inset *shows a posterior view of the azygos vein controlled by a vessel loop with the superior vena cava cannulated. The inferior vena cava is cannulated inside the pericardium as inferiorly as possible. The alternate approach is to cannulate the femoral vein and control the inferior vena cava with an umbilical tape inside or outside the pericardium.*

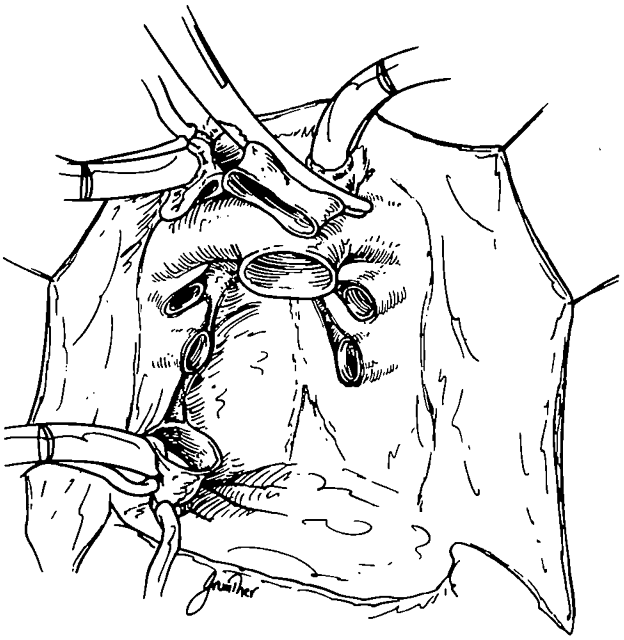

Fig 2. The heart-lung recipient after the recipient heart has been excised and preserved for implantation. Both the aorta and pulmonary artery were divided in their midportion, the superior vena cava was divided above the junction with the right atrium avoiding the sinoatrial node, and the inferior vena cava was divided above the inferior vena cava–right atrium junction leaving a rim of atrium on the inferior vena cava. Care is taken to have sufficient tissue at the ascending aorta, inferior vena cava, and superior vena cava stump for anastomosis.

is transected above the junction with the right atrium and the IVC is divided above the IVC–right atrial junction leaving a rim of atrial tissue on the IVC (Fig 2). The pulmonary veins are cut flush with the posterior pericardium and the heart is removed (Fig 3).

After removal of the donor heart, incisions are made posterior to the left and right phrenic nerves immediately anterior to the hilum; the incisions extend from the PA to the diaphragms. The left atrium is divided into a left and right half and the pulmonary veins are freed from the posterior connective tissue with careful preservation of the left vagus nerve and esophagus posteriorly. Careful hemostasis with both electrocautery and surgical staples is of paramount importance in the posterior mediastinum. The right and left PAs are transected. The bronchi are exposed, retracted well out toward the lateral chest wall, stapled, and transected (Fig 4). The trachea is exposed to the right of the aorta and transected immediately above the carina with careful preservation of surrounding blood supply.

The donor heart-lung block is passed onto the field and the donor trachea is unclamped and trimmed above the carina. The lungs are passed beneath the phrenic nerve pedicles (Fig 5). The tracheal anastomosis is then performed using continuous 3-0 polypropylene suture. The recipient's left PA is divided along its inferior surface and rotated 180 degrees to encircle the tracheal anastomosis. This flap is sutured into place using 5-0 polypropylene sutures. Hypothermic protection of the heart-lung block is

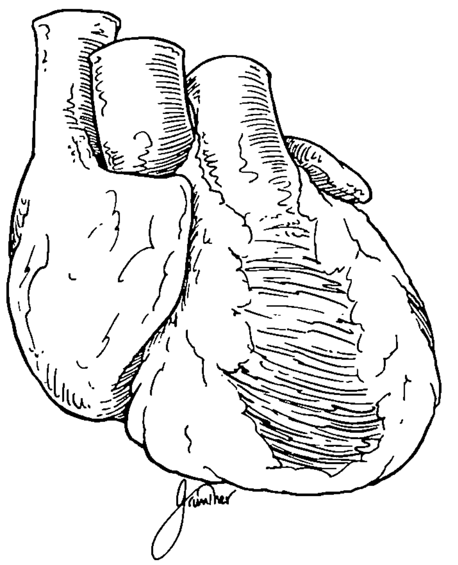

Fig 3. The excised cardiac allograft from the heart-lung recipient demonstrates the truncated inferior vena cava and the stump on the superior vena cava. The superior vena cava stump was suture-ligated with care to preserve the sinoatrial node. The inferior vena cava opening was extended along the crista terminalis to prepare the right atrium to right atrium anastomosis in the cardiac recipient.

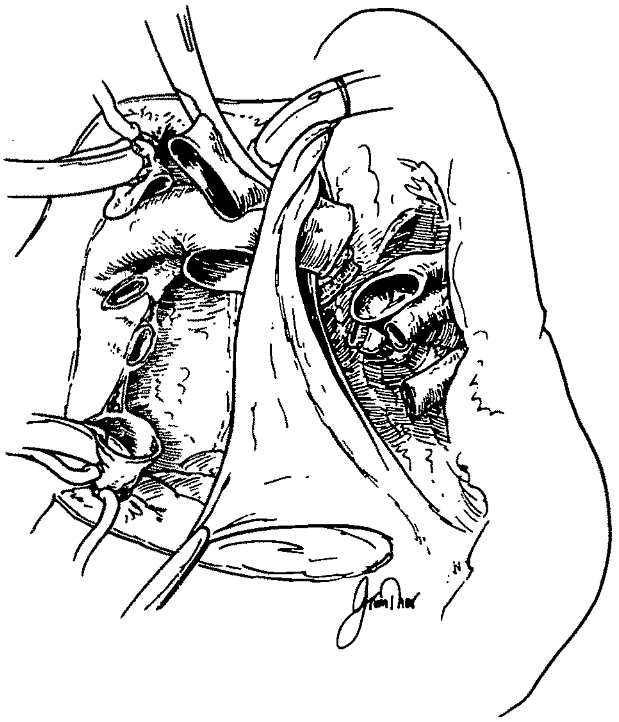

Fig 4. The pulmonary artery is transected as distally as possible to preserve it for later use as a pedicle flap to the tracheal anastomosis. Staple closure of the main bronchi allows for minimal contamination of the mediastinum. Avoid any damage to the esophagus and phrenic or vagus nerves.

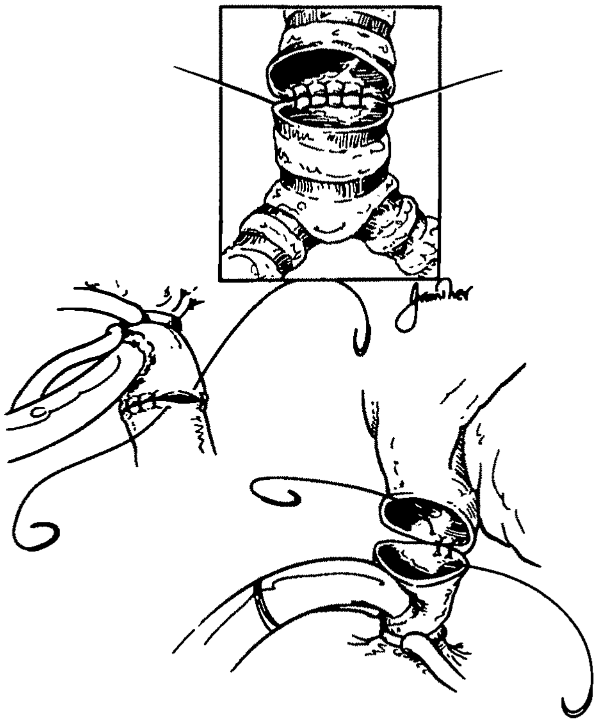

Fig 6. The three anastomoses in the heart-lung transplant procedure: the trachea, superior vena cava, and inferior vena cava. With the tracheal anastomosis the membranous portion is used to adjust for any size disparity. It is critical not to disrupt or injure the remaining blood supply to the trachea. Care is taken with the vena cava anastomosis to avoid any pursestringing of the anastomosis or twisting of the donor or recipient vessels.

maintained during implantation by continuous lavage with cold saline solution. The SVC, IVC, and aortic anastomoses are performed with running 4-0 polypropylene suture (Fig 6).

When all anastomoses are complete the chest is emptied of fluid and the caval snares are removed (Fig 7). The aortic cross-clamp is removed with the patient in the Trendelenburg position and air is removed from the heart via the aortic root vent site and a left ventricular puncture site. The patient is rewarmed and ventilated with 40% O_2

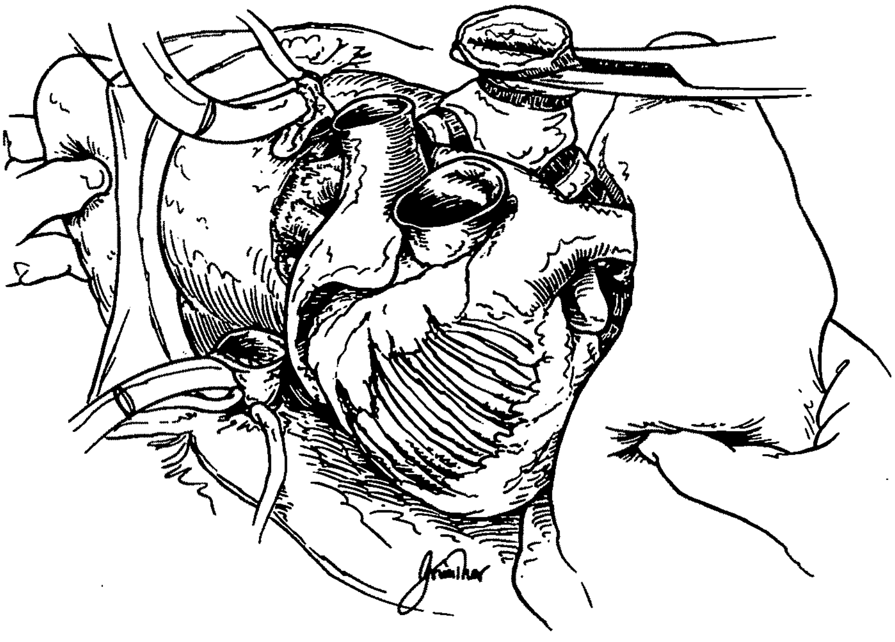

Fig 5. Donor heart-lung block being positioned into the heart-lung recipient. As the right or left lung, or both, is being passed beneath the phrenic pedicles, care must be taken to avoid any torsion of the main pulmonary or hilar vessels. At the same time the superior vena cava and inferior vena cava are aligned and trimmed to avoid any excess tissue. Tracheal tissue on the donor is trimmed to approximately 0.5 to 1.0 cm above the carina for anastomosis. Pleural space and size disparity between donor and recipient can be corrected in this maneuver by increasing or decreasing the length of the remaining recipient trachea before anastomosis.

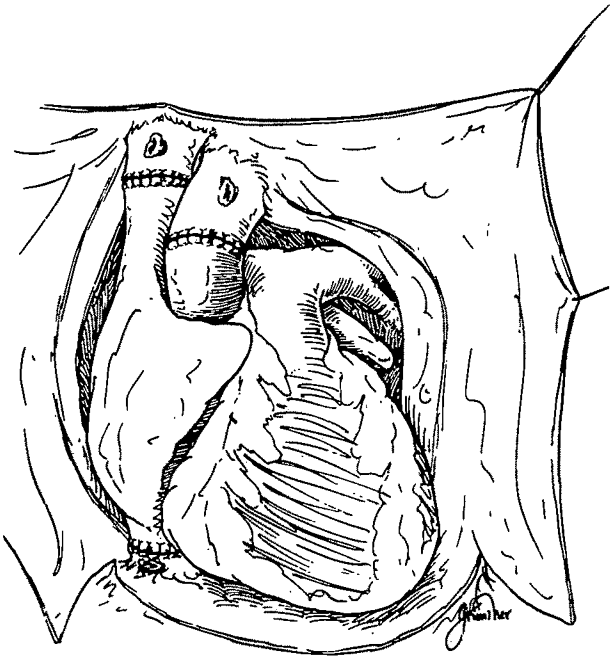

Fig 7. The completed heart-lung transplant procedure.

with 5 cm of positive end-expiratory pressure. Cardiopulmonary bypass is discontinued and isoproterenol is infused to maintain a heart rate of approximately 100 beats per minute.

Heart Recipient Operation

The donor heart is implanted in the recipient as described by Lower and Shumway [2], except for suture ligation of the SVC stump.

Results

At Temple University Hospital from May 1987 to January 1988 we have used this operative technique in the performance of three successful heart/heart-lung transplantations.

The paired heart-lung recipients/live heart donors and heart recipients were: a 27-year-old man with end-stage lung disease secondary to primary agammaglobulinemia with a 52-year-old woman with end-stage valvular heart disease; a 26-year-old man with end-stage lung disease secondary to cystic fibrosis with a 47-year-old woman with end-stage idiopathic cardiomyopathy; and a 21-year-old woman with end-stage lung disease secondary to cystic fibrosis with a 32-year-old man with end-stage idiopathic cardiomyopathy.

Table 1. Results of the Domino Procedure

Patient No.	Transplant Procedure Allograft	Length of Survival (days)	Complications
1	Heart-lung	590	Rejection, streptococcal pneumonia
2	OHT	72	Sepsis
3	Heart-lung	467	Sternal wound infection
4	OHT	467	None
5	Heart-lung	36	Rejection, cytomegalovirus penumonitis
6	OHT	358	None

OHT = orthotopic heart transplant.

Immediate graft function was demonstrated in all heart and heart-lung organs. There were no early or late surgical complications from the procedure. The follow-up is 65 months for all organs.

Among the heart recipients 1 patient died at 72 days secondary to systemic sepsis with intact allograft function; 1 heart-lung recipient died at 36 days secondary to cytomegalovirus pneumonitis. Complications among heart-lung recipients included two episodes of treated isolated pulmonary rejection, one episode of cytomegalovirus pneumonitis, one episode of streptococcal pneumonia, and one episode of superficial sternal wound infection (Table 1).

Comment

In the past heart-lung transplantation has been performed mainly for primary pulmonary hypertension and Eisenmenger syndrome. Today heart-lung and bilateral single-lung transplant procedures are being offered to patients with end-stage lung diseases but with no cardiac compromise. In such patients the heart is usually a viable organ for another patient. The domino procedure is another attempt to increase the cardiac donor pool.

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Simplified Technique for Open Placement and Removal of Intraaortic Balloon

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A rapid simplified technique for removal of a surgically placed intraaortic balloon is described.

(Ann Thorac Surg 1989;48:134–6)

Intraaortic balloon counterpulsation is an effective method of mechanical support in the postcardiotomy patient [1]. Previously, insertion of the balloon required surgical exposure of the common femoral artery and end-to-side anastomosis of a prosthetic graft to an artery [2]. Percutaneous placement of the balloon has shown to be as safe as the conventional technique [3], but is not always possible for those patients with soft femoral arteries or extensive adipose tissue or those on cardiopulmonary bypass in whom a femoral pulse is not palpable.

Direct placement of the percutaneous sheath in the common femoral artery can be accomplished after surgical exposure of the artery, rather than placement utilizing an end-to-side prosthetic graft. However, both the open transarterial and conventional graft technique require open removal and arterioplasty.

A technique is described for patients without clinically significant anterior common femoral artery plaques that simplifies balloon removal, thus enabling it to be done as a brief procedure in the Intensive Care Unit.

Technique

The common femoral artery is exposed through an oblique groin incision and is then punctured with a Cook or Cornan needle, and the J wire is threaded up the aortic arch (Fig 1). Progressive dilation of the arteriotomy is accomplished with graded plastic cannulas and then the deflated balloon is passed up to the appropriate distance. Intraaortic balloon pumping is established, and when satisfactory, a mattress or pursestring 5-0 monofilament suture is carefully placed around the introducer sheath (Fig 2). The sheath may be removed with a Datascope sheath stripper to allow more flow in smaller arteries. The suture is then secured with a short, 2-inch, red rubber Rummel tourniquet and is fixed in place with several metal clips placed so as not to damage the suture (Fig 3). The wound is then closed over the Rummel tourniquet and suture (Fig 4).

Removal of the balloon is performed under 1% Xylocaine (lidocaine) local anesthesia. The wound is prepared, draped, and opened. Systemic heparinization is not necessary in most cases as pumping is discontinued immediately before balloon removal. The tourniquet is released, the balloon is aspirated completely, and the balloon and sheath are then removed as a unit. The artery is flushed proximally and distally with digital pressure or vascular clamps (Fig 5). The previously placed suture is then tied with minimal narrowing of the artery. If a thrombectomy is required this can usually be performed

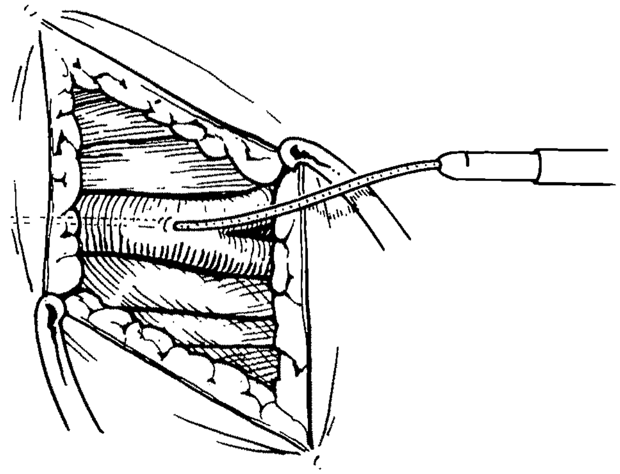

Fig 1. The dilator and introducer sheath are introduced over the guidewire into the exposed common femoral artery.

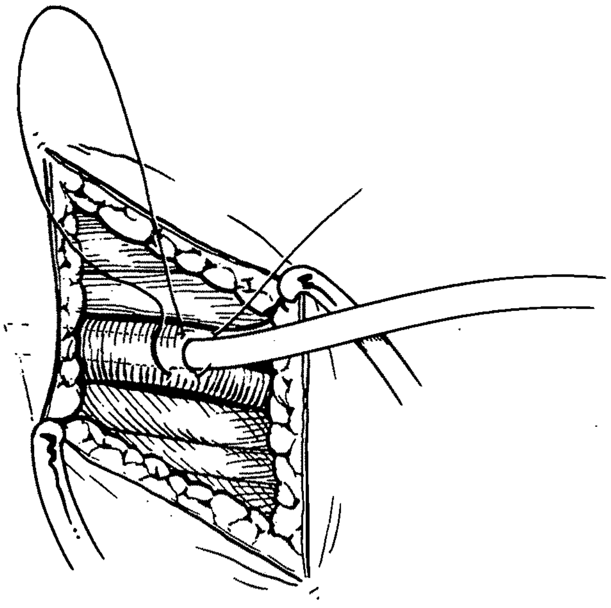

Fig 2. A pursestring suture is placed around the sheath.

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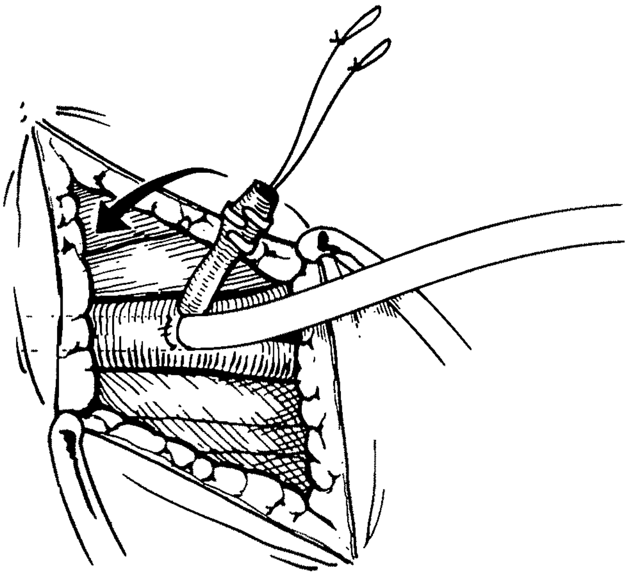

Fig 3. A Rummel tourniquet securing the pursestring suture is placed into the wound.

through the arteriotomy without disruption of the suture. Additional sutures, if necessary, are easily placed.

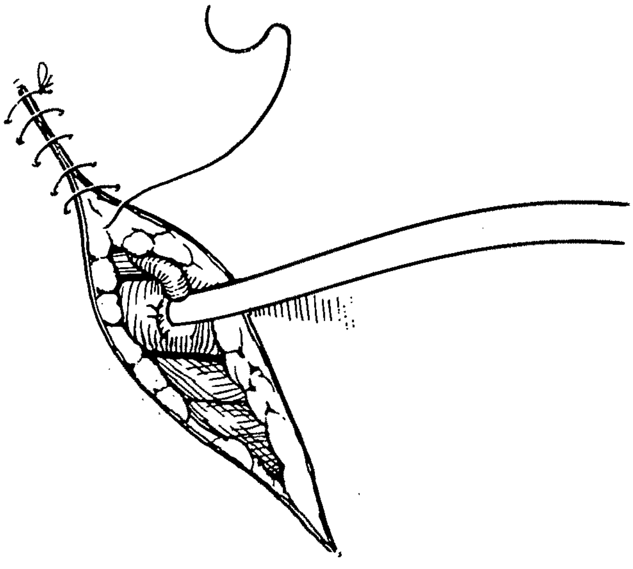

Fig 4. The wound is closed over the tourniquet.

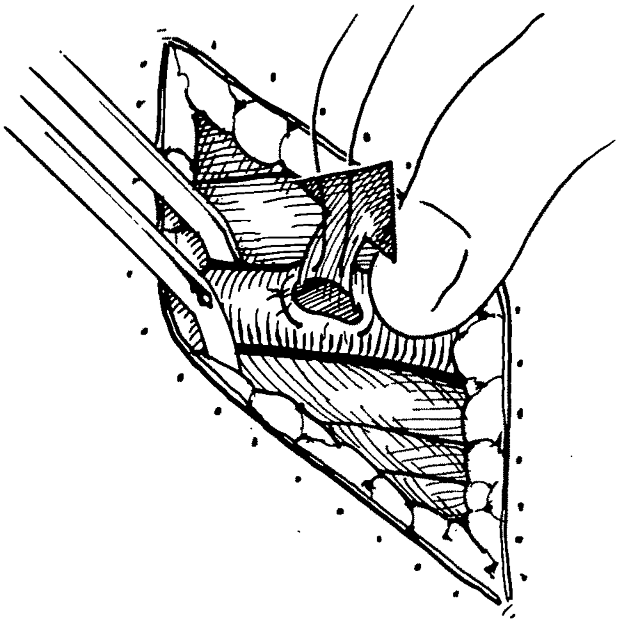

Fig 5. The balloon is removed and the femoral is artery flushed; the suture is tied.

Comment

This technique is expedient and applicable in many patients requiring open placement of the intraaortic balloon. It obviates scheduling delays with the operating room and additional major charges to the patient. Additionally, it may decrease thromboembolic complications related to restricted flow by the introducer sheath while maintaining hemostasis from the arteriotomy. This technique has been used in over a dozen patients to date with no complications observed.

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INVITED COMMENTARY

This article by Hebeler is timely, and the method described is appropriate to facilitate the insertion of balloons in obese people or in pulseless femoral arteries and to remove them without the need for a return to the operating room.

It is our practice in high-risk surgical patients to place at least a guidewire, if not a femoral arterial line, in these patients before induction of anesthesia. This wire is left in the sterile operative field and, in fact, can be used for monitoring. Should the need arise for intraaortic balloon pumping, even on cardiopulmonary bypass, the guidewire has already accessed the femoral artery, making percutaneous insertion easily possible. Certainly cutting down on the artery is a fairly safe technique, but as has been established previously, the balloon must then be removed directly by opening the wound and suturing the artery. Hebeler has described an innovative method of purse-string suture around the arteriotomy site to obviate the need for formal exploration of the artery and to convert the removal to a bedside technique. It should be stressed that when removing the percutaneous balloon and sheath, direct pressure should be applied distally to the femoral artery so that any embolic debris that is dislodged during the removal process will not embolize down the distal extremity.

The technique described will certainly make it easier to deal with these critically ill patients at the bedside in a safer fashion.

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Evolution of Surgical Treatment of Thoracic Aortic Aneurysms

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Aneurysms of the thoracic aorta remain a challenge to surgeons. My early experience began in 1950, when I excised a large aneurysm in one of Dr Alfred Blalock's patients. The patient survived and was cured. This experience convinced me that aortic aneurysms could be treated successfully by aggressive surgical means. Treatment, however, has changed from the early emphasis on excision of the lesion to the present belief in restoration of circulatory continuity using a suitable Dacron graft, or endoaneurysmorrhaphy.

(Ann Thorac Surg 1989;48:137–8)

Surgical treatment of aneurysms of the thoracic aorta has progressed strikingly during the past four decades, as surgeons have exercised their ingenuity, gained confidence in their technical skills, and employed new diagnostic and therapeutic devices and tools against these challenging lesions. Many of the successes in this field have gone almost unnoticed, however, when compared with the interest and excitement shown to cardiac surgery in general. Most of the accomplishments in the definitive and curative treatment of lesions of the thoracic aorta have occurred in the second half of this century.

While I was a resident in the Halsted Surgical Service at Johns Hopkins Hospital, I was confronted with a serious problem in one of Dr Alfred Blalock's patients, a 32-year-old man who was admitted to the hospital with a large, painful aneurysm in the right superior mediastinum. Several months earlier, the patient had been admitted for a right supraclavicular pulsation. He was found to have a postductal coarctation of the aorta. Dr Blalock excised and repaired the coarctation, hoping to forestall enlargement and inevitable rupture of the aneurysm. At the time of the second admission, Dr Blalock was enjoying a sojourn in Honolulu as a visiting professor. In his absence, the late Dr Mark Ravitch was the staff surgeon, and as rupture of the lesion seemed imminent, he gave me permission to proceed with operation on the aneurysm.

The operation that I performed on April 28, 1950, involved excision of the large aneurysm, including the sac, and ligation of the right subclavian artery proximally and distally. The patient survived and was cured. After Dr Blalock's return, in his usual modest and generous manner, he stated at Grand Rounds that he would not have had the courage to attempt excision.

Upon joining the surgical faculty at Baylor University College of Medicine in July 1951, I was confronted with a similar problem in a 46-year-old man who had a syphilitic aneurysm of the aortic arch that began at the origin of the innominate artery. This lesion was successfully resected, the arch was repaired, and the right subclavian and common carotid arteries were ligated. The patient survived and was cured. These 2 cases and a few others were reported before the Southern Surgical Association on December 1, 1951 [1].

This early experience convinced me that an aggressive approach to aortic aneurysms was justified and necessary. Emphasis in those early cases was placed on excising the aneurysm and restoring aortic continuity by a lateral aortorrhaphy. Among the limitations on excisional therapy at that time were the need to maintain cardiac function and continuous blood flow through the ascending and transverse aortic arch and lack of suitable graft materials. Thus, treatment in those early years had to be confined mostly to sacciform aneurysms in which a vascular clamp could be applied to the neck of the lesion and aortic continuity restored by a sutured aortorrhaphy. Introduction of temporary cardiopulmonary bypass in the mid-1950s overcame this major obstacle. Meanwhile, the introduction of synthetic fabric grafts of appropriate design and durability proceeded, permitting replacement of the thoracic aorta with assurance of long-term survival and minimal complications.

Of interest to me now is the transition from our original emphasis on *excision* of the lesion to the present belief in *restoration* of circulatory continuity using a suitable Dacron graft. Interestingly, Rudolph Matas, just over a century ago, described a method for repair of a peripheral arterial aneurysm and coined the term "restorative endoaneurysmorrhaphy" [2] for his procedure. That early concept is now the basis for much modern treatment of aneurysms of the thoracic aorta, ie, the sac is closed over the synthetic graft to avoid unnecessary mediastinal dissection and to control and reduce blood loss.

Especially challenging, and often frustrating during the early years, were lesions that involved the transverse aortic arch and the carotid and subclavian arteries. Various methods of preserving cerebral viability during such operations were attempted by us and others with unpredictable and inconsistent results. Shunts, which were used in an attempt to maintain physiological blood flow to the cerebrum, often led to complications resulting mostly,

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in my experience, from excessive flow into the delicate tissues of the brain. The introduction of hypothermic circulatory arrest using cardiopulmonary bypass has finally provided a more reliable means of dealing with such lesions. The optimum temperature needed to protect the brain for a period necessary to accomplish repair, however, remains unsettled. At very low levels of hypothermia, complications such as coagulopathy and other cold injuries may result. Our own experience has indicated that an induced temperature of 24° to 20°C suffices for most repairs in the transverse arch and provides 30 minutes of protection in a bloodless field [3]. As we gain further experience with this technique, we may find that some pharmacological adjuncts will ensure better cerebral protection during the ischemic period.

One challenge remains in the surgical treatment of thoracic aneurysms, ie, finding a method to repair lesions in the descending thoracic aorta that will consistently protect the spinal cord from ischemic injury—a complication dreaded by thoracic surgeons. As yet, none of the numerous methods that have been used or proposed give uniformly successful results. Hopefully, however, this final problem will also be resolved as surgeons continue to search for solutions to clinical problems with aortic aneurysms.

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Blunt Rupture of the Myocardium

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With the evolution of regional trauma systems, patients with severe cardiac injury are arriving in emergency departments with the potential for survival. This paper reviews the 61 survivors of nonpenetrating rupture of the free walls of the myocardium reported in the English-language literature. The chambers were involved in the following frequency: right atrium, 36; left atrium, 11; right ventricle, 12; and left ventricle, four. Most victims were young males, and 85% were involved in motor vehicle accidents. Seventy percent had an admission systolic blood pressure less than 80 mm Hg, 78% had distended neck veins or a central venous pressure greater than 20 cm H_2O, 67% had a widened mediastinum on admission chest roentgenogram, and 48% had fractures of the bony thorax. More than one hour elapsed before initiation of repair in 59%. Forty-eight percent of the repairs were performed via a median sternotomy. Cardiopulmonary bypass was used in only 10%.

(Ann Thorac Surg 1989;48:139–42)

"Few surgical emergencies present so great a diagnostic challenge or provide as great a therapeutic reward," wrote Driscoll [1] in 1973, in a discussion of nonpenetrating rupture of the heart. While it is estimated that blunt cardiac rupture accounts for 5% of the 50,000 annual highway deaths in the United States [2], survival from this injury is rare. The recent successful management of a patient with nonpenetrating rupture of the left ventricle, as well as the presentation of three nonsurvivors with blunt rupture of the heart, prompted this review.

History

The first description of rupture of the heart secondary to nonpenetrating trauma is variably credited to Borch in 1676 [3] or Akenside in 1753 [4, 5]. In 1826, Berard reported laceration of the left atrium in a young boy who fell from a window and died two and one-half hours later of tamponade [6].

Riolan first suggested pericardiocentesis for treatment of cardiac wounds in 1649. Larrey, surgeon for Napoleon, in 1829 performed the first pericardial drainage for cardiac tamponade; the patient, a soldier, survived [7].

The first successful cardiorrhaphy, for a penetrating wound, was reported by Rehn in 1897 [8, 9]. Over 50 years passed before Desforges and associates [10], in 1955, reported the first successful repair of a nonpenetrating cardiac rupture, in a male victim of a motor vehicle accident who sustained a tear of the right atrial–superior vena caval junction.

Incidence

Today, the majority of nonpenetrating lacerations of the myocardium occur due to motor vehicle accidents. Calhoon and associates [2], in a 1986 paper, estimated that blunt cardiac trauma accounted for 5% of the 50,000 annual highway deaths in the United States. Leinoff [11] and Kemmerer and co-workers [12], in separate autopsy series, reported a 4% incidence of cardiac laceration in victims of traffic accidents.

Three recent series addressed the incidence of cardiac rupture in blunt trauma [13–15]. In a review of 2,751 hospital admissions for blunt trauma, Martin and colleagues [13] reported cardiac rupture in 0.5%, half of whom survived. In two series of patients admitted for blunt chest injury, the incidence of blunt cardiac rupture was 2%, with no survivors [14, 15].

All four chambers of the heart are susceptible to rupture in nonpenetrating trauma. Bright and Beck [16], in 1935, reported an autopsy series of cardiac rupture due to blunt injury, with a similar frequency of involvement of each chamber: right atrium, 36; left atrium, 30; right ventricle, 31; left ventricle, 37; and two or more chambers, 13. Parmley and co-workers [17], in their 1958 autopsy series of nonpenetrating, traumatic myocardial rupture, found a preponderance of ventricular ruptures: right atrium, 41; left atrium, 26; right ventricle, 66; left ventricle, 59; and multiple chambers, 106.

Review of the English-language literature suggests that survival is more likely with atrial than ventricular rupture, and that right-sided lesions are more likely to be survived than left-sided lesions. A total of 61 survivors of rupture of the myocardial wall after nonpenetrating injury have been reported in the English-language literature. One survivor had rupture of both the right ventricle and right atrium [1], and another had rupture of the left ventricle and right atrium [18]. There have been reported 36 survivors of blunt right atrial rupture [1, 2, 4, 6, 7, 10, 13, 18, 19–33], 11 survivors of blunt left atrial rupture [13, 27, 29, 34–39], 12 survivors of blunt right ventricular rupture [1, 2, 13, 20, 28, 34, 40, 41], and 4 survivors of blunt left ventricular rupture [18, 34, 42, 43].

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Mechanism

On the basis of their autopsy series and laboratory experiments, Bright and Beck [16] proposed three mechanisms of cardiac rupture in nonpenetrating trauma: (1) bursting of the heart by compression between the sternum and vertebral column; considered most destructive if the force was applied when the heart was full, ie, at end-diastole or early systole, and if the force was directed from the base toward the apex; (2) increased intrathoracic pressure, either direct or indirect (eg, sudden compression of the legs and abdomen); and (3) contusion, with subsequent necrosis and softening of the myocardium, followed by delayed rupture hours to months after the injury.

In contrast to the third mechanism proposed by Bright and Beck, Barber [44], based on autopsy studies, believed delayed rupture to be a progression of endocardial laceration. He noted that the patients in his series were usually asymptomatic in the interval between their injury and subsequent rupture, and he suspected that symptoms would be manifested if a contusion or infarct were the primary lesion.

Motor vehicle accidents accounted for 85% of the patients who survived rupture of the heart from blunt trauma. Other mechanisms of injury include the striking of pedestrians by vehicles, crush injuries, and kicking or trampling by ungulates.

Right Atrial Rupture

The first successful surgical repair of blunt myocardial rupture was the repair of a right atrial injury by Desforges and co-workers in 1955 [10]. Since then, 35 additional survivors of nonpenetrating right atrial rupture have been reported [1, 2, 4, 6, 7, 13, 18, 19–33].

Several theories have been proposed to explain the fact that right atrial rupture is the most common lesion in survivors of blunt cardiac rupture. Myhre and associates [32] point out that the atrial appendages are the weakest part of the heart, implying greater susceptibility of atrial rupture. However, Bright and Beck [16] and Parmley and co-workers [17] demonstrated that all four cardiac chambers rupture with approximately equal frequency. Because of lower pressures in the atria, survival may be longer with atrial injuries [32, 39].

The appendage is the most common site of right atrial rupture; it is the site of rupture in 56% of survivors in whom the location of the lesion was specified. Atrial rupture also occurred across the right atrial–superior vena caval junction (28%) and across the right atrial–inferior vena caval junction (16%). Four patients had multiple atrial tears. The lacerations ranged from 1 to 8 cm in length.

Left Atrial Rupture

There have been only 11 reported survivors of left atrial rupture [13, 27, 29, 34–39]. The first successful repair of blunt left atrial rupture was reported by Bogedain and associates in 1966 [35]. The appendage was the site of rupture in 4 of 7 patients in whom the site was specified. Rupture extended into a pulmonary vein in 2 of 7 patients. The lacerations ranged from 1 to 5 cm in length.

Right Ventricular Rupture

Patrice reported the first successful repair of blunt right ventricular rupture in 1968 [41]. The first report in the English-language literature of a successful repair of a ventricular rupture secondary to nonpenetrating trauma was by Rotman and colleagues in 1970 [40]. Twelve successful repairs of blunt right ventricular rupture have been reported in the English-language literature [1, 2, 13, 20, 28, 34, 40, 41]. Driscoll [1] was the first to repair the simultaneous rupture of two cardiac chambers due to a nonpenetrating injury, in 1973. The patient sustained rupture of the right atrium and right ventricle in a motor vehicle accident.

Left Ventricular Rupture

Parmley and associates [17], in their 1958 autopsy series, reported 59 cases of left ventricular rupture, all of which were immediately fatal. Bright and Beck [16], however, in a 1935 autopsy series, reported that 10 of 37 victims of blunt left ventricular rupture survived for at least one hour, with deaths occurring from one hour to 7 weeks after injury.

Only 4 survivors of blunt left ventricular rupture have been reported [18, 34, 42, 43]. Aun and associates [42], in 1975, reported the first successful repair.

Diagnosis

Most victims of blunt cardiac rupture die promptly. However, in their 1935 autopsy series, Bright and Beck [16] found that 30 of 152 (20%) patients survived injury for one hour or more. Parmley and associates [17] reported 23 of 353 (6.5%) blunt cardiac ruptures were not immediately fatal, with 13 of 67 (19%) atrial ruptures not immediately fatal.

The diagnosis of these injuries, however, may be difficult. Most victims of blunt cardiac laceration have associated, more obvious injuries that may distract the physician. Parmley and associates reported that 50% of the patients in their series of cardiac rupture died primarily from associated, noncardiac injuries.

In part due to associated injuries, the usual findings of cardiac tamponade may be obscured. Beck's triad of muffled heart sounds, hypotension, and elevated central venous pressure is present in only one third of trauma victims with pericardial tamponade. Auscultation is difficult in a noisy emergency department, hypotension is often attributed to associated injuries, and hypovolemia can blunt the elevation of the central venous pressure [6]. In addition, pericardial laceration occurs in 10% to 33% of victims of blunt myocardial rupture [13, 45], so there may be no tamponade.

Thus, to diagnose these uncommon injuries, the physician must have a high index of suspicion of cardiac rupture in the blunt trauma victim. Getz and co-workers [6] stated that the following findings suggest myocardial laceration: (1) hypotension and hypovolemia out of proportion to the apparent injury; (2) hypotension and hypovolemia unresponsive to fluid resuscitation; (3) unremitting hemothorax despite pleural tube drainage and fluid resuscitation; (4) persistent metabolic acidosis despite fluid resuscitation; and (5) elevated central venous pressure or distended neck veins with hypotension despite fluid resuscitation. Combining the series of Patton and associates [27], who reviewed 24 blunt atrial injuries, and Williams and colleagues [34], who treated seven blunt cardiac ruptures, 100% of patients had hypotension, 90% had elevated central venous pressure or distended neck veins, and 92% were confused or in a coma. Analysis of the present review of survivors of blunt cardiac rupture showed 70% to have an admitting systolic blood pressure less than 80 mm Hg, and 78% to have a central venous pressure greater than or equal to 20 cm H_2O or distended neck veins.

Terry [46] suggested that cardiac injury should be suspected with sternal fracture, first rib fracture, fracture of seven or more ribs, or traumatic rupture of the diaphragm. As Barber and others have discussed, however, cardiac rupture may occur without fractures of the bones of the thorax, or even without bruising of the chest wall. Although this is true at any age, it is especially so in young patients with elastic chest walls [44]. In this review of survivors of blunt cardiac rupture, although 48% had some fracture of the bony thorax, 14% had chests that were described as "normal" (without fracture, abrasion, or contusion). Sixty-seven percent had enlargement of the cardiac silhouette or widening of the mediastinum on the initial chest roentgenogram.

Pericardiocentesis may help in the diagnosis and temporary treatment of cardiac rupture, but it is unreliable. The puncture may enter the cardiac chamber, yielding a false positive result. In addition, Sethia [47] reported a case of right atrial rupture without hemopericardium. Pericardiocentesis yielded 20 mL of yellow, clear fluid. Autopsy revealed a 2-cm tear in the right atrium, with two lacerations of the upper pericardium, through which 200 mL of blood had escaped into the superior mediastinum. In the relatively stable patient in whom the diagnosis of cardiac tamponade is suspected, a subxiphoid pericardial window, which may be extended to a median sternotomy if necessary, may more accurately diagnose cardiac rupture. However, in most reports, survival followed prompt thoracotomy or sternotomy. Definitive therapy of the unstable patient should not be delayed by diagnostic procedures.

There are no unequivocal signs of cardiac rupture. The major clinical signs suggestive of possible cardiac laceration include shock (hypoperfusion) that is unresponsive to aggressive intravenous fluid administration, neck vein distention, and elevated central venous pressure.

Treatment of Blunt Rupture of the Free Walls of the Heart

Median sternotomy offers the best exposure in the patient with blunt cardiac rupture [20]. The right atrium cannot be adequately examined through a left thoracotomy; median sternotomy offers superior exposure of both atria and is better tolerated by the patient. Argument in favor of left thoracotomy includes ease and quickness of access to the thoracic cavity with instruments readily available in the emergency department. In the reports of successful repair of blunt cardiac rupture, median sternotomy was used in 48%, left thoracotomy in 28%, bilateral transsternal thoracotomy in 20%, right thoracotomy in 5%, and left parasternal incision in 1 patient.

The surgical team and field should be prepared before the induction of anesthesia, as cardiac arrest often occurs upon induction [23]. Of the ten cardiac arrests in the reported survivors, five occurred in the operating room.

Control of the ruptured atrium can often be achieved with digital pressure or a vascular clamp, or by insertion of a Foley catheter through the rent with inflation of the balloon and traction on the catheter. Digital pressure will often control ventricular hemorrhage enough to allow placement of sutures beneath the fingers [34, 48]. If these measures are unsuccessful, and time permits, cardiopulmonary bypass may be necessary [49]. The first use of cardiopulmonary bypass in the repair of blunt rupture of a free wall of the heart was reported by Siderys and Strange in 1971 [24]. Cardiopulmonary bypass was used in only 10% of the reported successful repairs of nonpenetrating traumatic rupture of the free walls of the heart.

Prognosis

Mortality from blunt cardiac rupture is difficult to estimate. Although 61 survivors have been reported, there are few published series that provide a denominator from which to derive mortality figures. Mattox and associates [31], in 1975, reported an 85% mortality in 13 cases, and Shorr and co-workers [15], in 1987, reported a 100% mortality in 14 cases.

Analysis of reported survivors of nonpenetrating cardiac rupture reveals 76% are male and 69% are between the ages of 18 and 30 years. This probably represents more the overall sex and age distribution of blunt trauma victims than any specific survival advantage.

One third of the reported survivors of blunt cardiac rupture had an admission systolic blood pressure of 80 mm Hg or greater. On the other hand, one third had no detectable blood pressure on admission. Furthermore, 10 survivors experienced complete cardiac arrest, including 1 who arrested during transport to the hospital [21], 3 who arrested in the emergency room [1, 2, 22], 1 who arrested in the radiology department [25], and 5 who arrested in the operating room [2, 27, 30]. Thus, blood pressure at the time of presentation was not a valuable prognostic variable.

Pericardial tears are estimated to occur in 10% [13] to 33% [45] of all cases of blunt myocardial rupture. Hendel and Grant [18] suggested that laceration of the pericardium may favor temporary survival in blunt cardiac rupture by allowing partial release of tamponade while still controlling the bleeding to some extent. Our review lends support to this theory. The status of the pericardium is mentioned in the reports of 34 survivors, and the pericardium was lacerated in 9 (26%). Of reports in which the pericardium is discussed, the 3 patients with the longest intervals between injury and successful cardiorrhaphy (8.5 to ten hours) had laceration of the pericardium [10, 18, 38]. However, 4 patients with an intact pericardium survived from four to six hours between injury and repair [4, 20, 32, 37].

Summary

Blunt cardiac rupture accounts for an estimated 2,500 highway deaths per year in the United States [2]. To date, survival of blunt cardiac rupture is uncommon. The English-language literature contains reports of 36 survivors of right atrial rupture, 11 survivors of left atrial rupture, 12 survivors of right ventricular rupture, and 4 survivors of left ventricular rupture (2 patients had rupture of multiple myocardial chambers). With improved regional trauma systems and early recognition of these injuries, a higher rate of survival can be expected.

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Use of Conduits in Surgical Repair of Congenital Heart Disease

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CORRESPONDENCE

Myocardial Preservation: The Role of Magnesium

To the Editor:

We found the recent article by Keon and co-workers [1] of great interest. The study addresses an important clinical question, and the findings of this study could potentially influence procedures for cardiac transplant tissue transport. We therefore feel obligated to point out some fundamental observations that may be pertinent to the interpretation and potential clinical application of their findings.

Our general concern is with two aspects of the experimental design employed. First, cardiac transplant tissues are not usually transported in a solution as complete as Tyrode's medium. During harvesting, the coronary arteries of the heart are infused with a cardioplegic solution containing a high potassium concentration (10 to 20 mEq/L), and then the heart is immersed and transported in a cold (4°C) 0.9% saline solution. An experimental protocol that tests the effects of hypothermia in normal saline and then recovery in Tyrode's solution may be more meaningful.

Second, the magnesium ion concentration used in the control Tyrode's solution (3.1 mM) is approximately 3 to 4 times higher than is normally found in human blood or used by others [2–4] in in vitro experiments on human atrial tissue. Normal plasma magnesium concentration ranges between 1.5 and 2.1 mEq/L (0.75 to 1.05 mM), and most in vitro experiments on human atrial tissue use Tyrode's solutions containing 0.5 to 1.0 mM magnesium. This may be important in the interpretation of the results because elevated magnesium levels have been shown to have a wide variety of electrophysiological, contractile, and metabolic effects on cardiac function [5]. In particular, magnesium has been shown to have a protective effect on functional recovery after cardiac ischemia.

Hearse and associates [6] studied the protective effects of magnesium on rat heart function compromised by ischemic arrest. They found that increasing magnesium concentration in the infusate from 0 to 15 mM produced a progressive and significant improvement in the recovery of mechanical function during the reperfusion phase. This effect was already significant at concentrations within the range of 3.1 mM magnesium. In addition, they reported that magnesium had a similar protective effect on functional recovery from hypothermic (28°C) ischemic conditions, and that the protective effects of hypothermia and magnesium are additive. Hearse and associates suggest that elevated magnesium may be considered an important protective component of cardioplegic infusates. Therefore, interpretation of the results of Keon and co-workers must, at least, take into account the influence of the relatively high magnesium concentrations used. With these observations in mind, we believe that the findings of Keon and co-workers should be considered cautiously before changes in clinical protocols are undertaken.

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Reply

To the Editor:

My colleagues and I were pleased to receive the letter by Dr Lonchyna and Dr Lipsius. They raised interesting points that we would like to address. We certainly concur that our findings "should be considered cautiously before changes in clinical protocols are undertaken."

First, the methods used were designed to assess hypothermia alone. Our preparation had been optimized using the modified Tyrode's solution, so it was used for this experiment. We are also concerned about transport media and have undertaken a study to compare the recovery of atrial myocardium exposed to hypothermia in St. Thomas' cardioplegia, Krebs-Henseleit, Euro-Collins, and saline solutions. Preliminary results suggest that muscles exposed to saline solution have poorer recovery of function compared with muscles exposed to more balanced electrolyte solutions.

Concerning magnesium concentration, the modified Tyrode's solution was developed to optimize the performance of atrial myocaridum while in situ. Although elevated magnesium levels as used in this preparation have been shown to have protective effects that are additive with hypothermia, all muscles in this experiment were exposed to the same magnesium concentration. If magnesium was protective as suggested, then one may have expected that the lowest temperature should have resulted in the best recovery. This was not the case.

We would like to stress that the method used was designed to evaluate different temperatures for cooling myocardial tissue. Other variables including transport media and various possible additives must be assessed as well. It is our intent to carry on with these investigations in our own laboratory, and we hope that this work stimulates others to investigate optimal methods for donor heart preservation.

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Extraction of Cardiopulmonary Grafts

To the Editor:

We were interested to read of Dr Todd and colleagues' technique for extraction of cardiac and pulmonary grafts from a single donor [1]. However, we believe that this sequential excision of heart and lungs prolongs the procedure unnecessarily and may waste valuable organs.

We have used a cold flush technique and always extract both heart and lungs en bloc from the donor. This technique is rapid and allows dissection of the heart from the lungs to be completed at a side table out of the way of the retrieval teams for the abdominal organs. Left atrial anatomy is easily visualized during dissection of the lungs off the heart.

Over the past 18 months, we have performed eight single-lung and one double-lung transplantations. On all but one occasion,

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the heart from the donor was used successfully at another center in the United Kingdom. In addition, we have dispatched two separate donor lungs from one patient to another center and used the heart on one of our own recipients. All three organs on this occasion were implanted without difficulty and functioned well.

We have not found it necessary to dissect the interatrial groove when using the right lung or both lungs in addition to the heart. The relatively narrow atrial cuff remaining on the lung is easily sufficient for the atrial anastomosis.

The Toronto technique involves prolonged and inconvenient dissection on the table and usually the loss of one donor lung. We would suggest that a flush perfusion technique followed by side-bench separation of the heart and the two lungs is more convenient. In the current era, the use of only one lung is wasteful, and any technique that produces such waste is outmoded.

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Reply

To the Editor:

Dr Kirk and associates raise two important questions, and we appreciate the opportunity to respond. The first question is the advisability of sequential excision of heart and lungs in situ rather than a subsequent dissection on a side table after en bloc removal of the heart and lungs. Does the former unnecessarily prolong the procedure? In our procedure very little dissection is conducted before administration of cardioplegia. En bloc excision of the lungs follows the complete removal of the heart. The abdominal team is delayed by five to ten minutes. We contend that in situ sequential excision saves valuable time that we had previously found to be wasted on the side table. The separation of the heart is the same whether in situ or after en bloc heart/lung extraction. The orientation provided in situ is more familiar to most surgeons and thus not only is rapid but may be less liable to technical error. There is less chance that the separation procedure itself is prolonged and that either organ is damaged from unwarranted warm ischemia or excessive handling. The dissection of the interatrial groove is, in our opinion, an important adjunct. It is interesting to note that Dr Kirk and associates have performed only one double-lung transplantation after their reported method of donor extraction. It is particularly important for the double-lung graft that an adequate anterior cuff of left atrium be left on the right side. No doubt one can get away without it, but we contend that a superior atrial anastomosis is provided with the dissection of the interatrial groove. Certainly the latter is best done in situ with the heart full. Last, it is clear from the letter of Kirk and associates that a single team undertakes thoracic donor extraction in their institution. In North America both a cardiac and thoracic team are present at the extraction. Their efforts are, in our opinion, best coordinated at the operating table with in situ extraction.

The second question concerns the provision of two lung grafts and a heart graft from a single donor. Dr Kirk and associates imply that the technique as described "waste[s] valuable organs." We agree that each donor should provide the maximum number of organs and, indeed, so stated in the introduction to our paper. Our technique will easily provide all three grafts (two lungs and one heart). It is not the technique that limits their use, but rather the logistics of transplantation on a large continent with few pulmonary transplant centers. Because of our limited institutional resources we have not been able to implant two single lung grafts from a single donor, and there was unfortunately (as Dr Kirk and associates should know) no other active center in our country performing lung transplantation at the time the manuscript was written.

In short, we believe that the technique as described in our paper is the most efficient and rapid method of separate extraction of heart and lungs from a single donor. It will consistently provide a physiologically and anatomically sound organ for both cardiac and pulmonary transplantation teams.

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Use of Autologous Pericardium for Ventricular Aneurysm Closure

To the Editor:

Closure of the resected left ventricular aneurysm remains a test case for the suture technique and the quality of underlying tissue. The Teflon felt suture support, which distributes suture pressure, has become a welcome help by diminishing the risk of this operation. In regard to the article by Fiore and associates [1], my colleagues and I also were concerned about the "dire consequences of the indiscriminate use of Teflon felt pledgets" [2], and we have developed and introduced fabric tissue support that is resorbable [3]. In our group of patients we have not yet observed any infection; we believe that the resorption of the foreign material (PDS [polydioxanon], Vicryl [polyglactin]; Ethicon GmbH, Hamburg, Federal Republic of Germany) can prevent the risk of chronic infection of the suture line. The development of the resorbable suture support now allows full tailoring of the strip or patch.

Autologous pericardium is obviously the patient's own material, almost always available, and cheap. In some cases variable compliance and variable thickness and calcifications may render the use more difficult. Technically, a fresh piece of normal pericardium—a patch, strip, or pledget—is known for wrinkling at the most inappropriate place and time. Furthermore, the extreme stretching capacities of the pericardium may limit the mutual pressure distribution between the suture points.

Based on his clinical experience, Carpentier suggests immersing a piece of pericardium for one or two minutes in 5% glutaraldehyde solution before its use for congenital repairs. This quick procedure provides an excellent material to work with. The stiffened pericardium becomes uniform and easy to handle, more similar to the fascia lata suture support suggested in 1944 by Beck [4]. The fate of biological material treated in this way is well known due to the long follow-up available for cardiac bioprosthetic valves [5].

I believe that the choice of the ideal material to support sutures is difficult to make. For the time being the personal preference of the surgeon and the immediate possibilities will make the choice. Our preference remains for the resorbable material or, if pericardium is used, then for pericardium stiffened by glutaraldehyde solution.

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Right Heart Endocarditis and Endocardial Pacemakers

To the Editor:

Hong-Barco and associates [1] report a case of endocarditis due to endocardial pacemaker lead, and they note that "rarely cardiopulmonary bypass is required to manage the unyielding leads." We have had 4 cases of right heart endocarditis with endocardial pacemaker leads in which removing the leads by cardiopulmonary bypass was necessary for control of endocarditis. The endocarditis was present between 3 months and 3 years after implantation. Infection of the pacemaker pocket was the site of entry in 3 patients. One patient had no infection before endocarditis.

At operation, adherence of endocardial lead to the tricuspid valve was noted in 3 patients, in one instance with perforation of the tricuspid valve. All patients had atrial vegetations, and all are now well and free from infection.

Pacemaker pocket infection often can be managed with conservative measures, but if endocarditis develops, the pacing apparatus must be removed. Removal is usually achieved with traction devices, but for entrapped leads, cardiopulmonary bypass is the only recourse.

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Buckling in Bioprosthetic Valves

To the Editor:

The recent paper by Vesely and co-workers [1] shows the influence that gluteraldehyde tissue fixation under pressure has on the bending stresses and buckling in porcine aortic xenograft heart valves. Their observations are consistent with the work of Broom and Thomson [2] and Thubrikar and associates [3], who demonstrated that an increased elastic modulus and spatially fixed aortic root increases the bending stresses in the fully open valve leaflet.

However, these papers overlook two important factors in the design and function of porcine xenografts. First, fixation of leaflets under pressure alters not only the elastic modulus of the tissue, but also the dimensions and geometry of the unloaded leaflet, particularly in the radial direction. Second, bending strains are high when the leaflets are moving from the closed to the open position, so the actual deformations that occur during leaflet transposition are as important as the geometry of the fully open leaflets. Porcine xenografts fixed under pressure do not open in the same manner as the natural valve. The natural leaflet opens by reversing its curvature in the base first, producing an S shape radially in the leaflet, so minimizing the bending strains in the circumferential collagen fibers [4]. This method of opening occurs due to the geometry of the natural leaflet and the very low radial elastic modulus. Fixation under pressure (even at 2 to 4 mm Hg) increases the radial length of the leaflet, altering the unloaded leaflet geometry and producing a much smaller radius of curvature in the radial direction. As a consequence, fixed porcine leaflets open by reversing their curvature in the circumferential direction, so producing an S shape and high bending strains in the circumferential collagen fibers. The mechanism of opening and pressure required to open leaflets is highly dependent on the radius of curvature (proportional to R^{-3}) [5]; consequently, leaflet geometry is a very important factor in leaflet opening. Although an expanding aortic root and low elastic modulus are important factors in reducing strains, natural leaflet function with low circumferential bending stresses during transposition will not be achieved unless the geometry of the natural leaflets is maintained. This can be achieved using zero pressure (zero strain fixation) or by using fresh tissue as in frame-mounted homograft valves.

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Reply

To the Editor:

We agree with the comments of Dr Fisher and Mr Davies regarding the importance of properly maintaining valve geometry during fixation. This is certainly one of several factors affecting the in vivo performance and longevity of porcine xenograft bioprostheses. However, in our paper we set out to examine specifically the mechanism by which buckling damages the prosthetic materials. Buckling has been alluded to in several papers [1–3], but it has remained unclear whether such buckling is normal or abnormal or an undesirable process. We believe our paper provides some initial data on this topic.

Regarding Fisher and Davies' description of the mechanism of aortic valve opening, we apparently disagree on two points. Fisher and Davies cite Swanson and Clarke [1] to suggest that, during opening, the natural leaflet forms an S shape, reversing its curvature circumferentially. We have not come across any direct evidence that the leaflets behave in that manner. That study was purely theoretical and the mathematical model was based on assumptions that may have been valid in 1973, but are no longer applicable. Specifically, Swanson and Clarke assumed that the leaflets offer no resistance to the flow of blood and that they rotate about their point of attachment at the base of the aortic root. We have recently shown that both xenograft and natural aortic valve leaflets have a measurable bending stiffness [4] and therefore must offer a resistance to blood flow during the opening phase. Whether a reversal of curvature in the radial direction occurs or not, Swanson and Clarke did not explicitly state or hypothesize that reversals of curvature in the radial direction reduce circumferential bending stresses. In fact, Fisher and Davies suggest that fixed porcine leaflets "reverse their curvature in the circumferential direction" and produce "high bending strains in the circumferential fibers." We do not believe that reverse radial bending acts in any way to reduce circumferential stresses.

Fisher and Davies promote the use of stent-mounted homograft valves. Clinical experience clearly shows, however, that stent-mounted homografts suffer from stress concentrations at the stent/tissue interface [5]. In contrast, freehand implanted allografts have performed very well [6]. We believe that a factor contributing to the success of the freehand allograft is the *absence* of a stent. The commissures of the unstented valve are free to move apart during the systolic expansion of the aortic root, pull along the free edge of the leaflet, and thus reduce the sharp reversals of circumferential curvature that normally occur in stented valves. If implanted properly by a skilled surgeon, the unstented allograft more closely mimics the function of the natural valve. Indeed, we expect that stents with fixed-diameter annuli will eventually be phased out in favor of expansile stents or stentless xenograft bioprostheses.

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THE SOCIETY OF THORACIC SURGEONS

Twenty-fifth Anniversary Meeting
September 11–13, 1989
Baltimore Convention Center, Baltimore, Maryland

The Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons will be held at the Baltimore Convention Center on September 11–13, 1989, preceded by the Twenty-third Postgraduate Program on Sunday, September 10. The meeting is open to all duly qualified physicians. Both members and nonmembers are urged to register in advance of the meeting.

The 1989 Program Committee is very pleased with the large number of abstracts submitted for this special meeting of The Society. The high quality of the abstracts along with the increased number made possible the development of a program that represents all aspects of adult and pediatric cardiac surgery and general thoracic surgery.

Several innovations have been planned for the program. On Monday afternoon, three parallel sessions will replace the usual single session. One parallel session will be devoted to general thoracic surgery and another will be split between pediatric cardiac surgery and transplantation. The third session will be a research forum; a large number of research abstracts were submitted for this part of the program.

The popular Tuesday morning problem case presentations and the Wednesday morning clinical workshops will continue.

The Committee also had a significant increase in the number of movies and video tapes submitted for the Annual Movie Night, making it possible to develop an excellent program representative of all aspects of the specialty.

Also, in celebration of 25 years of achievement in cardiothoracic surgery, two retrospectives will be delivered by noted experts Dr David B. Skinner and Dr John W. Kirklin.

Registration and Fees

An advance registration form with hotel reservation information and details regarding spouses' activities will be mailed to Society members. Nonmembers should write to the Secretary, George C. Kaiser, MD, The Society of Thoracic Surgeons, 111 E Wacker Dr, Chicago, IL 60601.

Members are not required to pay a registration fee for the Scientific Program. Residents and fellows may register without payment of a registration fee upon presentation of a letter from their chief of service. The fee for other physicians is $200, except guest speakers, authors, coauthors, and invited discussants. Nurses and paramedical personnel may register upon payment of a $35 registration fee and presentation of a letter of introduction from a Society member.

The Postgraduate Program is sponsored by the Committee on Postgraduate Education of The Society. Registration fee for the Postgraduate Program is $60 for all physicians, residents, and fellows, which includes a luncheon.

There will be no advance registration for the concurrent Problem Case Presentations on Tuesday, September 12, or the Clinical Workshops on Wednesday, September 13. Attendance will be by ticket only, and each seminar is limited to 35 physicians. Tickets can be purchased at the Society's registration desk on Monday, September 11, starting at 12:30 PM. The price of the ticket covers attendance at the seminar and a continental breakfast.

Presentation and Publication

Papers presented at the Scientific Session must be submitted to the Secretary at the time of presentation, or may be submitted to the Editor prior to the meeting for possible earlier publication.

Speakers for the Scientific Sessions should limit their presentations to 10 minutes. They are requested to meet with the projectionist in the preview room prior to the opening of their session to prepare their slides for presentation.

Those who wish to discuss a paper may write the Secretary prior to the meeting. Discussants from the floor should submit their names to the Moderator at the podium prior to the opening of the session during which the paper is to be presented. Discussants from the floor are limited to 2 minutes; primary discussants are limited to 3 minutes.

Discussants will receive a copy of their remarks shortly after the Annual Meeting. Any delay in the return of the corrected discussion to the Editor will hold up publication of the paper. Timely response of all authors and discussants is, therefore, urged since delays are unfair to those who promptly return their material for publication.

Accreditation

The Society of Thoracic Surgeons is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. One credit hour in Category I of the Physician's Recognition Award of the American Medical Association may be claimed for each hour of participation by the individual physician. The Postgraduate Program is authorized for eight hours of Category I CME credit.

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TWENTY-THIRD POSTGRADUATE PROGRAM
THE SOCIETY OF THORACIC SURGEONS

Sunday, September 10, 1989
Baltimore Convention Center, Baltimore, Maryland

8:00–12:00 **Morning Session**

8:00 Introduction to the 1989 Postgraduate Course
Adnan Cobanoglu, Portland, OR, Co-Chairman, Postgraduate Committee

I. Mini Symposium: Congenital Heart Surgery
Moderator: Adnan Cobanoglu, Portland, OR

8:10 Transposition of the Great Arteries
William G. Williams, Toronto, Ont, Canada

8:30 Tetralogy of Fallot
Winfield J. Wells, Los Angeles, CA

8:50 Atrioventricular Canal
Adnan Cobanoglu, Portland, OR

9:10 Homograft Valves and Conduits in Congenital Heart Surgery
Kevin Turley, San Francisco, CA

9:30 Panel Discussion: Questions and Answers

9:45 **II. Pacemakers: Update 1989**
Seymour I. Furman, New York, NY

10:15–11:00 Coffee Break: Visit Exhibits

11:00 **III. C.C.C.E.T.S Basic Science Lecture***
Introduction
Gerard A. Kaiser, Miami, FL, Co-Chairman, Coordinating Committee for Continuing Education in Thoracic Surgery

Platelet and Neutrophil Activation in Experimental and Clinical Cardiopulmonary Bypass
Robert W. Colman,** Director, Thrombosis Research Center, Temple University School of Medicine, Philadelphia, PA

12:00–1:30 Luncheon

Luncheon Address: Oncogenes in the Pathogenesis of Lung Cancer
John D. Minna,** Chief, Navy Medical Oncology Branch, National Cancer Institute, Bethesda, MD

1:30–5:00 **Afternoon Session**

IV. Management of Carcinoma of the Esophagus
Moderator: Joseph I. Miller, Atlanta, GA, Co-Chairman, Postgraduate Committee

1:30 Options in Surgical Resection
Robert J. Ginsberg, Toronto, Ont, Canada

1:50 Role of Radical Resection in Esophageal Carcinoma
Mark K. Ferguson, Chicago, IL

2:10 Role of Brachytherapy
Bill Nelems, Vancouver, BC, Canada

2:30 Role of Neoadjuvant Therapy
David Kelsen,** New York, NY

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* Open Session
**By Invitation

2:50 Panel Discussion: Questions and Answers

3:00–3:45 Coffee Break: Visit Exhibits

V. Difficult Problems in Coronary Artery Surgery
Moderator: Kent W. Jones, Salt Lake City, UT

3:45 Patients Without Conduits
Andrew S. Wechsler, Richmond, VA

4:00 The "Bad" Ventricle
Stanley K. Brockman, Philadelphia, PA

4:15 Ischemic Mitral Regurgitation
Cary W. Akins, Boston, MA

4:30 Postinfarction Ventricular Septal Defect
Kent W. Jones, Salt Lake City, UT

4:45–5:00 Panel Discussion: Questions and Answers

PROGRAM
TWENTY-FIFTH ANNIVERSARY MEETING
THE SOCIETY OF THORACIC SURGEONS

September 11–13, 1989

September 11, 1989 (Monday)
Morning

7:45 Welcome
Dr John M. Dennis, Vice President for Academic Affairs, University of Maryland School of Medicine
Dr Richard S. Ross, Dean of the Medical Faculty, The Johns Hopkins University School of Medicine
The Honorable Kurt Schmoke, Mayor of Baltimore
Dr Vincent L. Gott, Chairman, Committee on Local Arrangements

8:15–11:15 **Scientific Session**

1. **J. Maxwell Chamberlain Memorial Paper**

   Wound Complications After Coronary Bypass Surgery With Vein Grafts Only, One Internal Thoracic Artery Graft, or Two Internal Thoracic Artery Grafts
   Floyd D. Loop, Bruce W. Lytle, Delos M. Cosgrove III, Saade Mahfood, Marlene Goormastic, Robert W. Stewart, Leonard A. R. Golding, and Paul C. Taylor, Cleveland, OH

2. Long-Term Results of Total Repair of Tetralogy of Fallot
   Peter J. Horneffer, Kenneth G. Zahka, Stuart A. Rowe, Teri A. Manolio, Bruce A. Reitz, Catherine A. Neill, Langford Kidd, and Timothy J. Gardner, Baltimore, MD

3. Ventricular Septal Defect Associated With Aortic Valve Incompetence: Comparative Results of Two Groups Undergoing Conservative Surgical Management
   Sylvain Chauvaud, Alain Serraf, Charles DuBost, and Alain Carpentier, Paris, France

9:10–9:30 **Special 25th Anniversary Address**

Technical and Scientific Advances in General Thoracic Surgery Over the Past 25 Years
David B. Skinner, New York, NY

4. Surgical Management of Automatic Atrial Tachycardias
   Paul J. Hendry, Douglas L. Packer, Mark D. Plunkett, Mark P. Anstadt, and James E. Lowe, Durham, NC

5. Can Computed Tomography of the Chest and Adrenal Glands Stage Lung Cancer? Yes and No
   Joseph W. Lewis, Jr, Jay L. Pearlburg, Gordon H. Beute, Michael V. Alpern, and Paul A. Kvale, Detroit, MI

6. Left Ventricular Ejection Fractions Following Multiple Percutaneous Transluminal Coronary Angioplasties
Robert H. Zeff, Mark Spector, Chamnahn Kongtahworn, David Gordon, L. A. Iannone, T. M. Brown, Mark McGaughey, William Wickemeyer, James R. Skinner, and Steven J. Phillips, Des Moines, IA

11:15–12 Noon **Presidential Address**
George G. Lindesmith

Afternoon

1:30–5:00 **Parallel Scientific Sessions**
Session I

1:30–2:45 **Thoracic**

7. Esophagectomy for Esophageal Disruption
Mark B. Orringer and Mack C. Stirling, Ann Arbor, MI

8. Survival After Surgical Resection for High-Grade Chest Wall Sarcomas
Roger R. Perry, Steven A. Rosenberg, David Venzon, Jack A. Roth, and Harvey I. Pass, Bethesda, MD

9. Cervical Exenteration
Douglas J. Mathisen and Hermes C. Grillo, Boston, MA

10. The Role of Brachytherapy in the Management of Advanced Chest Malignancies
Joseph W. Lewis, Jr, Young C. Bae, Paul A. Kvale, and Donald J. Magilligan, Jr, Detroit, MI

3:30–5:00 **Thoracic**

11. The Effect of Antireflux Surgery on Barrett's Mucosa
Warren A. Williamson, F. Henry Ellis, Jr, Peter S. Gibb, David M. Shahian, and Thomas H. Aretz, Boston, MA

12. Indications for Esophagectomy in Nonmalignant Barrett's Esophagus
Nasser K. Altorki, David B. Skinner, Andrea Segalin, Mark K. Ferguson, and Alex G. Little, New York, NY

13. Reoperation for Thymoma
Paul A. Kirschner, New York, NY

14. Survival After Conservative Resection for T1 N0 M0 Non-Small Cell Primary Lung Cancer
Raymond C. Read, Gordon Yoder, and Robert C. Schaefer, Little Rock, AR

15. Cancer Recurrence After Resection: T1 N0 Non-Small Cell Lung Cancer
Paul A. Thomas, Jr, and Lawrence H. Rubinstein, Chicago, IL, for The Lung Cancer Study Group

Session II

1:30–2:45 **Congenital Heart Disease**

16. Management of Neonatal Critical Pulmonary Stenosis in the Balloon Valvotomy Era
Joseph Caspi, John G. Coles, Lee N. Benson, Robert M. Freedom, Patricia E. Burrows, George A. Trusler, and William G. Williams, Toronto, Ont, Canada

17. Technical Considerations in Correction of Total Anomalous Pulmonary Venous Connection Below the Diaphragm
Steven J. Phillips, Chamnahn Kongtahworn, Robert H. Zeff, James R. Skinner, Basaviah Chandramouli, and John H. Gay, Des Moines, IA

18. Subaortic Stenosis: When to Operate?
E. Charles Douville, Robert M. Sade, Fred A. Crawford, Jr, and Henry B. Wiles, Charleston, SC

19. Shone's Anomaly: Operative and Late Outcome
Mark Iannettoni, Macdonald Dick II, Amnon Rosenthal, Steven F. Bolling, and Edward L. Bove, Ann Arbor, MI

3:30–5:00 **Transplantation**

20. HLA Histocompatibility Affects Cardiac Transplant Rejection and May Provide One Basis for Organ Allocation
Verdi J. DiSesa, Paul Kuo, Keith Horvath, Gilbert Mudge, John J. Collins, Jr, and Lawrence H. Cohn, Boston, MA

21. Pediatric Heart Transplantation With Triple-Drug Immunosuppression
Elizabeth A. Braunlin, Rebecca Diekmann, W. Steves Ring, and R. Morton Bolman III, Minneapolis, MN, and St. Louis, MO

22. Experience With Univentricular Support in Mortally Ill Cardiac Transplant Candidates
Robert L. Kormos, John Armitage, Harvey Borovetz, Robert L. Hardesty, and Bartley P. Griffith, Pittsburgh, PA

23. Direct Revascularization of Bronchial Arteries for Lung Transplantation: An Anatomical Study
Hans H. J. Schreinemakers and Joel D. Cooper, St. Louis, MO

24. The Influence of Omental, Intercostal Muscle, and Internal Mammary Artery Pedicled Grafts on Revascularization and Healing of Bronchial Anastomoses
Mark W. Turrentine, Kenneth A. Kesler, Cameron D. Wright, Keith E. McEwen, Phillip R. Faught, Mark E. Miller, Yousuf Mahomed, and John W. Brown, Indianapolis, IN

Session III

1:30–2:45 **Research**

25. Pulmonary Lobar Transplantation in Neonatal Swine
Timothy M. Crombleholme, N. Scott Adzick, Michael T. Longaker, Scott M. Bradley, Brian W. Duncan, Edward D. Verrier, and Michael R. Harrison, San Francisco, CA

26. Dynamic Aortomyoplasty to Assist Cardiac Failure
Juan C. Chachques, P. A. Grandjean, E. C. Fischer, T A. Pfeffer, C. Latremouille, I. Bourgeois, and Alain Carpentier, Paris, France

27. An Implantable Rate-Responsive Counterpulsation Assist System
Carlos Li, Andrew Hill, Mike Colson, Carolyne Desrosiers, and Ray Chu-Jeng Chiu, Montreal, Que, Canada

28. The Role of Triiodothyronine (T3) in Recovery of the Stunned Myocardium: A Randomized Blind Study in Dogs
Dimitri Novitzky, Nora Matthews, Richard Shawley, David K. C. Cooper, and Nazih Zuhdi, Oklahoma City, OK

3:30–5:00 **Research**

29. Localization of Spinal Cord Blood Supply During Aortic Operation
Lars G. Svensson, Vasishta M. Patel, Joseph S. Coselli, and E. Stanley Crawford, Houston, TX

30. Cerebrospinal Fluid Drainage and Steroids Provide Better Spinal Cord Protection During Aortic Crossclamping Than Does Either Modality Alone
Thomas T. Woloszyn, Corrado P. Marini, Matthew S. Coons, Ira M. Nathan, Anthony J. Acinapura, and Joseph N. Cunningham, Jr, Brooklyn, NY

31. Computerized Mapping of the Atrial Septum in Patients With AV Node Reentry, Atrial Flutter, and Septal Accessory Pathways
Byung-Chul Chang, Richard B. Schuessler, Constance M. Stone, Barry H. Branham, Thomas E. Canavan, John P. Boineau, Michael E. Cain, Peter B. Corr, and James L. Cox, St. Louis, MO

32. Relationship Between Total Mechanical Energy and Oxygen Consumption in Stunned Myocardium
Satoshi Furukawa, Joseph E. Bavaria, Gerhard Kreiner, and L. Henry Edmunds, Jr, Philadelphia, PA

33. Effects of Standard Mitral Valve Replacement on Left Ventricular Function
David H. Harpole, J. Scott Rankin, Walter G. Wolfe, W. Glenn Young, Jr, Peter VanTright III, and Robert H. Jones, Durham, NC

Evening

8:00–10:00 **Surgical Motion Pictures**
Moderators: Fred A. Crawford, Jr, Charleston, SC, and Gordon F. Murray, Morgantown, WV

1. Pulmonary Switch (Ross Procedure)
William W. Angell, James H. Oury, and Donald Ross, La Jolla, CA

2. First-Stage Palliation for the Hypoplastic Left Heart Syndrome
Randall B. Griepp, Jan D. Galla, and M. Arisan Ergin, New York, NY

3. Transbronchoscopic Closure of a Bronchopleural Fistula Using Fibrin Glue With Proximal Balloon Catheter Occlusion
Thomas L. Matthew, Todd A. Meyerhoffer, William H. Lindsey, William D. Spotnitz, and Thomas M. Daniel, Charlottesville, VA

4. Total Thoracic Aortic Replacement Using Composite Sutureless Intraluminal Ring Prostheses
Mehmet C. Oz, Robert C. Ashton, M. K. Singh, Kathleen W. McNicholas, and Gerald M. Lemole, New York, NY

5. Treatment of Advanced Esophageal Carcinoma With an Atkinson Tube
Carolyn E. Reed and John M. Kratz, Charleston, SC

6. Modified Cabrol Procedure for Ascending Aortic Replacement
C. D. Williams, Thomas H. Hoffmann, Robert E. Casali, Ruel N. Wright, and John H. Selby, Jr, Little Rock, AR

7. Sleeve Pneumonectomy for Bronchogenic Carcinoma
William Piccione, Jr, and L. Penfield Faber, Chicago, IL

8. Aortic Valvuloplasty for Aortic Insufficiency Secondary to Leaflet Prolapse
Delos M. Cosgrove III, Philip J. Currie, and William J. Stewart, Cleveland, OH

September 12, 1989 (Tuesday)
Morning

Breakfast Sessions

7:00–8:00 Problem Case Presentations (see pp 156–8 for program)

8:15–9:30 **Scientific Session**

34. Extension of Donor Criteria in Cardiac Transplantation: Surgical Risk Versus Supply-Side Economics
Michael S. Sweeney, David E. Lammermeier, O. Howard Frazier, Hans M. Haupt, and J. Michael Duncan, Houston, TX

35. Primary Tracheal Tumors: Results of Treatment
Hermes C. Grillo and Douglas J. Mathisen, Boston, MA

36. Heart Valve Surgery in Patients With Active Infective Endocarditis
Tirone E. David, Paulo Brofman, David Wong, and Christopher M. Feindel, Toronto, Ont, Canada

37. Valve Repair in Acute Endocarditis
Gilles Dreyfus, Alain Serraf, Victor A. Jebara, Alain Delcche, Jean-Paul Couetil, Sylvain Chauvaud, and Alain F. Carpentier, Paris, France

10:15 **Special 25th Anniversary Address**

Technical and Scientific Advances in Cardiac Surgery Over the Past 25 Years
John W. Kirklin, Birmingham, AL

10:35–12 Noon **Scientific Session**

38. Ten-Year Experience With the Porcine Bioprosthetic Valve: Interrelationship of Valve Survival and Patient Survival in 1,051 Valve Replacements
Ellis L. Jones, Victor E. Corrigan, Joseph M. Craver, Robert A. Guyton, Caryn Cohen, and William S. Weintraub, Atlanta, GA

39. Diaphragmatic Plication for Unilateral Diaphragmatic Paralysis: A 10-Year Experience
D. R. Graham, D. K. Kaplan, C. C. Evans, C. R. K. Hind, and R. J. Donnelly, Liverpool, England

40. Evolving Patterns in the Surgical Treatment of Malignant Ventricular Tachyarrhythmias
John A. Elefteriades, William P. Batsford, Lynda Rosenfeld, Lee L. Biblo, Richard W. Henthorn, Albert L. Waldo, and Alexander S. Geha, New Haven, CT, and Cleveland, OH

41. Thoracic Aortic Aneurysms After Acute Type A Aortic Dissection: Necessity for Follow-up
Markus Heinemann, Joachim Laas, Matthias Karck, and Hans Georg Borst, Hannover, West Germany

42. Valve Replacement in Infective Endocarditis in Patients With Septic Cerebral Emboli
Windsor Ting, Norman A. Silverman, and Sidney Levitsky, Chicago, IL

Afternoon

1:30–2:45 **Scientific Session**

43. Aortic Valve Surgery Following Percutaneous Balloon Valvuloplasty
Jatinder S. Dhillon, Robert G. Johnson, Robert D. Safian, Robert L. Thurer, and Ronald M. Weintraub, Boston, MA

44. Ten-Year Experience With Aortic Valve Replacement in 482 Patients 70 Years of Age or Older: Operative Risks and Long-Term Results
Aubrey C. Galloway, Stephen B. Colvin, F. Gregory Baumann, J. N. Slater, E. A. Grossi, F. M. Spiegel, Susan Harty, Alfred T. Culliford, E. Glassman, and Frank C. Spencer, New York, NY

45. Initial Report of the Veterans Administration Preoperative Risk Assessment Study for Cardiac Surgery
Frederick L. Grover, Karl E. Hammermeister, Cecil Burchfiel, and Veterans Administration Cardiac Surgeons, San Antonio, TX

46. Infusion of Nifedipine Following Coronary Artery Bypass Grafting Decreases the Incidence of Early Postoperative Myocardial Ischemia
Rainald Seitelberger, W. Zwölfer, Sebastian Huber, Friedrich Peschl, Josef Spatt, Christoph Holzinger, Heinz Weber, Helmut Pürerfellner, and Ernst Wolner, Vienna, Austria

3:30–5:00 Business Meeting (members only)

Evening

7:00 **Reception for Members and Guests**

September 13, 1989 (Wednesday)
Morning

7:00–8:00 **Breakfast Session**
Clinical Workshops (see p 158 for program)

8:30–12:30 **Scientific Session**

47. Routine Use of the Left Internal Mammary Artery Graft in the Elderly
Timothy J. Gardner, Peter S. Greene, Mary F. Rykiel, William A. Baumgartner, Douglas E. Cameron, Alfred S. Casale, Vincent L. Gott, Levi Watkins, and Bruce A. Reitz, Baltimore, MD

48. Seventeen-Year Experience With Bilateral Internal Mammary Artery Grafts
David L. Galbut, Ernest A. Traad, Malcolm J. Dorman, Paul L. DeWitt, Parry B. Larsen, Paul A. Kurlansky, Jaclyn H. Button, Joan M. Ally, and Thomas O. Gentsch, Miami, FL

49. Results of Internal Mammary Artery Grafting Over 15 Years: Single Versus Double Grafts
Andrew C. Fiore, Keith S. Naunheim, Philip A. Dean, George C. Kaiser, D. Glenn Pennington, Vallee L. Willman, Lawrence R. McBride, and Hendrick B. Barner, St. Louis, MO

50. Risks of Bilateral Internal Mammary Artery Bypass Grafting
Nicholas T. Kouchoukos, Thomas H. Wareing, Suzan Murphy, Cheryle Pelate, and William G. Marshall, Jr, St. Louis, MO

51. Clinical Experience With Mini-Tracheostomy
John C. Wain, Donna J. Wilson, and Douglas J. Mathisen, Boston, MA

52. Retrograde Coronary Sinus Cardioplegia for Aortic Valve Surgery: A Clinical Report on 500 Patients
Philippe Menasché, Jean-Baptiste Subayi, and Armand Piwnica, Paris, France

53. Chemotherapy and Radiation Therapy Prior to Transhiatal Esophagectomy for Esophageal Carcinoma
Mark B. Orringer, Arlene A. Forastiere, Claudia Perez-Tamayo, Susan Urba, and Bonnie J. Takasugi, Ann Arbor, MI

54. Skeletonization of the Atrioventricular Node in 23 Patients: Surgical Alternative for AV Node Reentrant Tachycardia
Gerard Guiraudon, George Klein, Arjun Sharma, Raymond Yee, and Osamu Fujimura, London, Ont, Canada

55. Effect of Intraoperative Plasmapheresis on Blood Loss and Homologous Transfusion in Cardiac Surgery
James W. Jones, Tim A. McCoy, Robert A. Rawitscher, and David A. Lindsley, Toledo, OH

56. Intraoperative Management of Patients With Heparin-Induced Thrombocytopenia: The University of Pennsylvania Experience
Jeffrey R. Kappa, Carol A. Fisher, Patrice Bell, Fred Campbell, Norig Ellison, and V. Paul Addonizio, Philadelphia, PA

September 12, 1989 (Tuesday morning)

7:00–8:00 PROBLEM CASE PRESENTATIONS
(10 Simultaneous Sessions)
Session Committee: Delos M. Cosgrove III, and Alexander S. Geha, Cleveland, OH

SEMINAR I
PULMONARY PROBLEMS
Discussion Leader: Blair A. Keagy, Chapel Hill, NC

1. Mediastinopleuroscopy for Paravertebral Lung Cancer to Confirm Unresectability and Avoid Major Thoracotomy
Robert G. Carlson and Emmett Mackan, Temple, TX

2. Massive Hemoptysis in a Young Man with a Normal Chest Roentgenogram
Hani Shennib, David S. Mulder, Jim Wilson, and Ray Chu-Jeng Chiu, Montreal, Que, Canada

3. Swan-Ganz Catheter-Induced Hemoptysis and Pulmonary Artery False Aneurysm
William Feng, Arun K. Singh, Thomas Drew, and Walter Donat, Providence, RI

SEMINAR II
PULMONARY INFECTIONS
Discussion Leader: Joseph I. Miller, Atlanta, GA

4. Massive Bronchopleural Fistula due to Aspergillosis in a Patient With Lymphoma
Howard Langstein and Harvey I. Pass, Bethesda, MD

5. Surgical Techniques and Considerations in Complex Bronchopleural Fistula Involving Atypical Mycobacterial Infection
George B. Haasler, Milwaukee, WI

6. Invasive *Aspergillus* with Bronchopleural Fistula Complicating Surgery and Radiation Therapy for Bronchogenic Carcinoma
Thomas R. J. Todd, Toronto, Ont, Canada

SEMINAR III
TRACHEAL PROBLEMS
Discussion Leader: Arthur N. Thomas, San Francisco, CA

7. Amyloidosis of the Trachea
Carolyn M. Dresler and F. Griffith Pearson, Toronto, Ont, Canada

8. Severe Complication of the Monier-Kuhn Syndrome
Harold C. Urschel, Jr, Dallas, TX

9. Recurrent Tracheoesophageal Fistula After an Apparently Successful Repair With Muscle Interposition in a Ventilator-Dependent Patient
Robert B. Wagner, Willie C. Blair, and Talal Munasifi, Rockville, MD

SEMINAR IV
ESOPHAGEAL PROBLEMS
Discussion Leader: Alex G. Little, Las Vegas, NV

10. Therapy for Cervical Esophageal Cancer
Haywood S. Gilliam and Victor A. Ferraris, San Francisco, CA

11. Instrumental Perforation in a Patient With Suspected Carcinoma of the Distal Esophagus: Late Presentation
John R. Hankins, Baltimore, MD

12. Impacted Esophageal Foreign Body
Leslie J. Kohman, John A. Meyer, and Marcy A. Bernstein, Syracuse, NY

SEMINAR V
PROBLEMS IN THORACIC TRAUMA
Discussion Leader: Norman J. Snow, Cleveland, OH

13. Exclusion Versus Repair of Thoracic Esophageal Injuries
David Duncan and John D. Rumisek, Jacksonville, FL

14. Traumatic Ventricular Septal Defect and Transected Thoracic Aorta
Robert F. Tranbaugh, Deborah L. Manjoney, and Joseph N. Cunningham, Jr, Brooklyn, NY

15. Transection of the Innominate Artery With Dissection of the Aortic Arch
Harold L. Lazar, Gaetano Paone, Ahmad Rajaii, and Richard J. Shemin, Boston, MA

SEMINAR VI
PROBLEMS IN VALVULAR HEART DISEASE
Discussion Leader: Cary W. Akins, Boston, MA

16. Perforation of the Ventricular Free Wall Following Balloon Valvuloplasty
George E. Cimochowski, Ramon A. Cukingnan, and Joseph S. Carey, Torrance, CA

17. Double-Valve Replacement for Right-Sided Carcinoid Heart Disease
Alejandro Aris, Jorge Juliá, José M. Padró, and José M. Caralps, Barcelona, Spain

18. Evaluation and Treatment of Drug-Resistant Vegetative Endocarditis
John D. Rumisek and Eric L. Ceithaml, Jacksonville, FL

SEMINAR VII
PROBLEMS IN ACQUIRED HEART DISEASE
Discussion Leader: Delos M. Cosgrove III, Cleveland, OH

19. Critical Aortic Stenosis and Asymptomatic Pulmonary Lesion
Charles C. Canver, Thomas Z. Lajos, and Robert M. Mentzer, Jr, Buffalo, NY

20. Left Thoracotomy for Combined Coronary Bypass Grafting and Repair of Descending Thoracic Aortic Aneurysm
Gregory S. Couper, Lawrence H. Cohn, and John J. Collins, Jr, Boston, MA

21. Replacement of an Infected Bentall Homograft
Glorianne Ropchan and Tirone E. David, Toronto, Ont, Canada

SEMINAR VIII
PROBLEMS OF THE GREAT VESSELS
Discussion Leader: Alexander S. Geha, Cleveland, OH

22. Mycotic Aneurysm of the Aortic Arch with Aortoesophagotracheal Fistula
Joshua H. Burack, Joseph Lamelas, Mario Sabado, Robert F. Tranbaugh, and Joseph N. Cunningham, Jr, Brooklyn, NY

23. Acute Aortic Dissection Presenting With Evidence of Bowel Ischemia and Tamponade
Lynda L. Mickleborough, Steven E. Fremes, and Akihiko Usui, Toronto, Ont, Canada

24. Infected Ascending Aortic Aneurysm
John H. Lemmer, Jr, and Douglas M. Behrendt, Iowa City, IA

SEMINAR IX
PROBLEMS IN TRANSPLANTATION
Discussion Leader: R. Morton Bolman III, Minneapolis, MN

25. Single Lung Transplantation and Closure of Patent Ductus Arteriosis for Eisenmenger's Syndrome
Steven E. Fremes, G. Alexander Patterson, William G. Williams, Bernard S. Goldman, and the Toronto Lung Transplant Group, Toronto, Ont, Canada

26. Advanced Mechanical Support Combining ECMO and Biventricular Assist as a Bridge to Transplantation
    Mark Guadagnoli, Larry Wei, Robert Kormos, Thomas Gasior, John Armitage,
    Robert L. Hardesty, and Bartley P. Griffith, Pittsburgh, PA
27. Cardiac Transplantation for Intractable Prosthetic Valve Endocarditis
    Verdi J. DiSesa and Lawrence H. Cohn, Boston, MA

SEMINAR X
PROBLEMS IN CONGENITAL HEART DISEASE
Discussion Leader: Scott Stewart, Rochester, NY

28. Life-Threatening Postoperative Junctional Ectopic Tachycardia in an Infant
    Paul W. Braunstein, Robert M. Sade, and Paul C. Gillette, Charleston, SC
29. Tetralogy of Fallot and Absent Pulmonary Valve Syndrome: Primary Repair in a 7-Week-Old Baby
    C. I. Tchervenkov and Anthony R. C. Dobell, Montreal, Que, Canada
30. Pulmonary Atresia and Intact Ventricular Septum: Complicated Fontan Operation 11 Years After Waterston Shunt
    G. Ziemer, M. Heinemann, A. Haverich, I. Luhmer, H. C. Kallfelz, and Hans G. Borst,
    Hannover, West Germany

September 13, 1989 (Wednesday morning)

7:00–8:00 CLINICAL WORKSHOPS
(8 Simultaneous Sessions)
Session Committee: Robert A. Guyton, Atlanta, GA, and Douglas J. Mathisen, Boston, MA

WORKSHOP I
HOMOGRAFT AND AUTOGRAFT REPLACEMENT OF THE AORTIC VALVE
Ronald C. Elkins, Oklahoma City, OK

WORKSHOP II
MECHANICAL LEFT VENTRICULAR ASSISTANCE
O. Howard Frazier, Houston, TX

WORKSHOP III
CARDIAC TRANSPLANTATION IN INFANTS
Constantine Mavroudis, Chicago, IL

WORKSHOP IV
MEDIASTINAL WOUND INFECTIONS
Thomas J. Vander Salm, Worcester, MA

WORKSHOP V
CURRENT THERAPEUTIC APPROACHES TO CARCINOMA OF THE LUNG
Harvey I. Pass, Bethesda, MD

WORKSHOP VI
BRONCHOPLASTIC TECHNIQUES FOR AIRWAY RECONSTRUCTION
Douglas J. Mathisen, Boston, MA

WORKSHOP VII
THERAPY FOR FAILED ANTIREFLUX PROCEDURES
Mark B. Orringer, Ann Arbor, MI

WORKSHOP VIII
LUNG TRANSPLANTATION
Joel D. Cooper, St. Louis, MO

THE ANNALS OF THORACIC SURGERY
Official Journal of The Society of Thoracic Surgeons and the Southern Thoracic Surgical Association

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Third Annual Meeting of the European Society for Vascular Surgery, Malmö, Sweden—September 3–5, 1989

A satellite symposium on pharmacological intervention to increase patency in arterial reconstructions will be held in the same location on September 6–7, 1989. For information on both symposia, contact the Congress Organisation Bureau, ESVS 89, c/o ICM AB, Geijersgatan 50, S-216 19 Malmö, Sweden.

Nineteenth World Congress of The International Society for Cardiovascular Surgery, Toronto, Ontario, Canada—September 5–9, 1989

For information on this meeting, contact XIX World Congress, ISCVS Administrative Offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Fourth World Congress of the International Society for Diseases of the Esophagus, Chicago, Illinois—September 6–8, 1989

This meeting is sponsored by the American College of Chest Physicians and Smith Kline & French Laboratories and is accredited for hour-to-hour credit in category 1 of the Physician's Recognition Award of the AMA. For information, contact the American College of Chest Physicians, PO Box 93826, Chicago, IL 60673.

The Third Current Controversies & Techniques in Congenital Heart Surgery, Baltimore, Maryland—September 8–9, 1989

Sponsored by the University of Nebraska Medical Center. For information on this meeting, contact Terry Slade Young, Current Controversies and Techniques in Congenital Heart Surgery, 11 S Paca St, University Square Bldg, Suite 304, Baltimore, MD 21201; or telephone (301) 328-2399 (facsimile: (301) 328-8514).

Twenty-fifth Annual Meeting of The Society of Thoracic Surgeons, Baltimore, Maryland—September 11–13, 1989

For information on this meeting, contact George C. Kaiser, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Thirty-eighth Annual Meeting of The Scandanavian Association for Thoracic and Cardiovascular Surgery and The Scandanavian Society for Extracorporeal Technology, Aarhus, Denmark—September 13–16, 1989

For information on this meeting, contact the Secretary of the Congress Committee SATCVS/SCANSECT, Chr. Mouritzen, MD, Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus-Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

Third Annual Meeting of the European Association for Cardio-Thoracic Surgery, Munich, Federal Republic of Germany—October 9–11, 1989

For information on this meeting, contact Organizing Secretariat, Interplan Convention and Visitor Service, Sophienstrasse 1, D-8000 Munich 2, FRG; or telephone 089 59 44 92 (telex: 523183 iplan d; facsimile: 089 59 16 10).

Sixth World Congress of Bronchoesophagology, Tokyo, Japan—October 15–18, 1989

This meeting is sponsored by the Organizing Committee of the Sixth World Congress of Bronchoesophagology, the Japan Broncho-esophagological Society, and the Foundation for Advancement of International Science under the auspices of the International Bronchoesophagological Society. For information, contact the Secretariat of the Sixth

World Congress of Bronchoesophagology, c/o Japan Convention Services, Inc, Press Center Bldg, 2-2-1 Uchisaiwaicho, Chiyoda-ku, Tokyo 100, Japan; or telephone 03-508-1213 (telex: J33104; facsimile: 03-508-0820).

American College of Surgeons, Atlanta, Georgia—October 15–20, 1989

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050.

Sixteenth World Congress on Diseases of the Chest and the Fifty-fifth Annual Scientific Assembly, American College of Chest Physicians, Boston, Massachusetts—

October 30–November 3, 1989

This meeting is sponsored by the American College of Chest Physicians and the International Academy of Chest Physicians and Surgeons. For information, contact the American College of Chest Physicians, 911 Busse Highway, Park Ridge, IL 60068; or telephone (312) 698-2200.

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association, Scottsdale, Arizona—November 9–11, 1989

For information on this meeting, contact Gordon F. Murray, MD, Southern Thoracic Surgical Association, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Sixty-second Scientific Session of the American Heart Association, New Orleans, Louisiana—November 13–16, 1989

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 750-5300.

Twenty-fifth Anniversary—Open Heart Surgery, Jerusalem, Israel—December 28, 1989–January 1, 1990

For information on this meeting, contact Joseph B. Borman, MD, or the Secretariat, PO Box 32390, Jerusalem 91323, Israel; or telephone 972-2-663171 (telex: 26205 TRGBL IL; facsimile: 972-2-665277).

Specialty Review in Thoracic Surgery, Chicago, Illinois—January 8–13, 1990

This course is sponsored by the Cook County Graduate School of Medicine and is accredited for approximately 47 hours in category 1 of the Physician's Recognition Award of the AMA. For information, contact the Registrar's office: within Illinois, 1 (800) 621-4649; outside Illinois, 1 (800) 621-4651.

Nineteenth Annual Meeting of the German Society for Thoracic, Cardiac, and Vascular Surgery, Bad Nauheim, Federal Republic of Germany—February 22–24, 1990

For information on this meeting, contact Hagen D. Schulte, MD, Professor of Surgery, Department of Thoracic and Cardiovascular Surgery, Heinrich-Heine-University, Moorenstrasse 5, D-4000 Dusseldorf, Federal Republic of Germany.

Aortic Surgery Symposium II, New York, New York—May 4–5, 1990

This symposium is sponsored by Meadox Medicals, Inc, and is accredited for 15 hours in category 1 of the Physician's Recognition Award of the AMA and toward the New York Medical Association Certificate in Continuing Medical Education. For information, contact Beverly Farrier, Symposium Coordinator, ProMedica International, 620 Newport Center Drive, Suite 575, Newport Beach, CA 92660.

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 440 Park Avenue South, New York, NY 10016 (telephone: (212) 684-5540; facsimile: (212) 545-0651). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $15.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3695). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad. To respond to an anonymous ad, write to Box Number, *The Annals of Thoracic Surgery*, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

SITUATIONS AVAILABLE

Cardiovascular and thoracic surgeon, board eligible or certified, wanted to join another surgeon in private practice in the Southeast. Please respond with curriculum vitae.

Please respond to Box 100. 100A/G

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae and names of references.

Please respond to Box 102. 102G/C

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland, OR 97213-2282. 124C/I

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV.

Please respond to Box 105. 105C/H

Cardiothoracic surgeon to join established group in northwest Indiana (very near Chicago). Excellent salary. Please respond with curriculum vitae.

Please respond to Box 104. 104C/H

Cardiothoracic surgeon wanted for busy, expanding Southeastern private group in regional medical center with university affiliation. Practice includes most aspects of adult and pediatric cardiac and thoracic surgery. Surgeon must be board eligible or certified with contemporary training. Excellent opportunity for suitable applicant.

Please respond to Box 112. 112D/G

Cardiovascular/thoracic surgeon for expanding 2-man practice in northwest Florida. Primarily adult cardiac surgery, doing 350–400 cases per year. Please respond with curriculum vitae and references.

Please respond to Box 137. 137E/G

Cardiothoracic surgeon, BE/BC, to join established 2-man private practice involved with adult cardiac, thoracic, and vascular surgery in major Midwest community. Salary leading to partnership. Please send CV, clinical experience, and references.

Please respond to Box 143. 143E/G

Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits. Respond with curriculum vitae.

Please respond to Box 144. 144E/D

Cardiothoracic surgeon needed to join established 2-man group in practice of adult cardiac, pulmonary, and vascular surgery. Must be board certified or eligible and graduate from a US medical school.

Please respond to R. W. Ruess, MD, 1834 Broadway, Cape Girardeau, MO 63701. 149E/G

Cardiothoracic surgeon/BC/BE: to establish a cardiothoracic surgery practice in 29-doctor multispecialty group practice. Local 579-bed hospital has received C.O.N. for cardiac surgery. Competitive salary and incentive plus benefit package. Located in Central Florida, lake country.

Please respond to Box 150. 150E/G

Cardiovascular surgeon, board certified or eligible, needed for busy, private established practice. Primarily open heart surgery with some peripheral vascular and thoracic surgery. Competitive salary and benefits. Respond with CV and cover letter.

Please respond to Box 151. 151FG

Recruiting thoracic/vascular surgeon, VA Medical Center, Clarksburg, West Virginia. Affiliated with West Virginia University. Full surgical residency rotation. Dual appointment.

Respond to Gordon Murray, MD, Professor and Chairman, Department of Surgery, West Virginia University Medical Center, Morgantown, WV 26505; or telephone (304) 293-4869. Equal opportunity employers. 146FG

Cardiothoracic surgeon: Board certified or eligible is sought to join an academic practice in the Midwest. Opportunity to become active and contribute to a growing cardiothoracic transplantation program. Excellent research opportunities available.

Direct curriculum vitae or inquiries to J. Terrance Davis, MD, Medical College of Ohio, C.S. #10008, Toledo, OH 43699. An equal opportunity employer. 153F/I

Cardiothoracic surgeon wanted to join a 2-man group located in an excellent growing community on the southeast coast of Florida. Practice mainly adult cardiac. BC/BE candidate with access to Florida license. Send CV.

Please respond to Palm Beach Heart Surgery, 3385 Burns Rd, Suite 106, Palm Beach Gardens, FL 33410. 152FG

Cardiovascular and thoracic surgeon BC/BE needed to join a busy solo CVT surgeon in private practice. Prefer recent grad.

Special expertise in adult and congenital/pediatric heart surgery a must. Desirable SW location. Please submit curriculum vitae and three professional references.

Please respond to Box 155. 155FG

Cardiovascular and thoracic surgeon, BE/BC, wanted to join a busy private practice in Pittsburgh, PA. Please respond with curriculum vitae and details of experience.

Please respond to Box.157. 157F/H

Cardiovascular and thoracic surgeon—ABTS certified, wanted to join active adult and pediatric cardiovascular surgery practice in metropolitan DC area. Practice includes arrhythmia and vascular surgery, and cardiac transplantation. Respond with curriculum vitae outlining training and recent surgical experience.

Please respond to Box 156. 156FG

Thoracic-vascular surgeon: Excellent opportunity for a board-certified or board-eligible noncardiac thoracic-vascular surgeon to join group practice on south shore of Long Island. Associated with two large level II 400-bed hospitals, fine recreational facilities, including beaches and boating, quality schools, and excellent homes.

Please respond to Box 148. 148EGIKA

Cardiac-thoracic surgeon, needed for expanding program on west coast of Florida. Excellent opportunity, private practice, primarily adult cardiac including cardiac transplantation. BC/BE required. Please send CV.

Please respond to Box 173. 173G

Cardiothoracic/vascular surgeon wanted to join established practice in Ohio. Recent graduate preferred. Please submit curriculum vitae and three references.

Please respond to Box 172. 172G/K

Cardiac surgeon needed for growing open heart program. Our service area encompasses more than 200,000 people in the intermountain West. Our program offers an extremely modern practice in Idaho's newest and largest referral center. Commutes average 10 minutes on uncrowded country roads. Recreation opportunities include some of the Rockies' finest skiing, hunting, fishing, camping, and hiking. For the right board eligible/certified cardiovascular surgeon, this position combines a fully supported cardiac practice with big country living.

Please respond to Box 174. 174G/I

Academic cardiothoracic surgeon. The Division of Cardiovascular and Thoracic Surgery at the University of South Florida is seeking applications for a full-time faculty position. This is an excellent opportunity for academic and clinical development in an expanding program. Superb facilities and a most desirable location further enhance the position.

Please forward curriculum vitae and three letters of recommendation to Peter P. McKeown, MB, FRCS(C), Chief, Division of Cardiovascular and Thoracic Surgery, University of South Florida, 12901 Bruce B. Downs Blvd, Box 16, Tampa, FL 33612-4799. The University of South Florida is an equal employment opportunity/affirmative action employer. 171G

Thoracic surgeon: Board certified or eligible. Interested in practice of thoracic, vascular, and general surgery in the greater Cincinnati area. Send resume.

Please respond to Box 170. 170G/I

Senior Investigator. A position of Senior Investigator in the Surgery Branch, National Heart, Lung, and Blood Institute will be available in November 1989. The responsibilities include independent performance of a wide range of cardiac operations including CABG, valve, valve + CABG, simple congenital, and IHSS procedures. The position requires the conduct of clinical and laboratory research and the teaching of midlevel general surgery residents and interaction with post CT residency fellows. The applicant must have completed an approved cardiothoracic surgery residency training program and have 2–5 years experience as an independent cardiac surgeon. A strong academic background is sought in all applicants. The base salary range is $60,000–78,000 depending on qualifications. Physicians may be eligible for additional bonuses.

Interested potential applicants should write or call Richard E. Clark, MD, Chief, Surgery Branch, NHLBI, Building 10, Room 2N244, 9000 Rockville Pike, Bethesda, MD 20892; (301) 496-4285. US Citizenship required. NIH is an equal opportunity employer. 169G

Cardiovascular thoracic surgeon needed to join busy established private practice in Ft. Lauderdale, Florida. Recent graduate preferred, must be board eligible or certified. Please send CV.

Please respond to Box 168. 168G

Cardiac transplant surgeon: Major cardiac surgery center with university affiliation and approved residency program in east coast city seeks board certified thoracic surgeon with heart transplant experience to direct the transplant program. Full open heart practice and partnership opportunity offered as well. Excellent salary and benefits. Please send curriculum vitae.

Please respond to Box 166. 166GH

Cardiovascular and thoracic surgeon, board eligible or certified, to join expanding practice in Rocky Mountain region. Salary leading to full partnership. Please send CV and references.

Please respond to Box 165. 165G/J

Excellent opportunity for a BC/BE pediatric cardiac surgeon and BC/BE pediatric cardiologist to be involved in expanding a successful adult cardiac program in the upper Midwest. This is a cooperative venture between a medical school and a private practice adult cardiology group, so that opportunity for full- or part-time academic appointments in addition to private practice is available. Located in a family oriented community with excellent outdoor recreational facilities including hunting, fishing, and water sports. Send CV.

Please respond to Box 164. 164G

Cardiovascular and thoracic surgeon: Position available for a board certified or eligible cardiovascular and thoracic surgeon to join a 3-man private practice involved with adult cardiac, thoracic, and peripheral vascular surgery in a desirable eastern metropolitan area. Association will lead to competitive salary, excellent fringe benefits, and early partnership. Please send curriculum vitae.

Please respond to Box 163. 163G

Thoracic and cardiovascular surgeon, board certified or eligible, wanted for an established practice in the Midwest with experience in adult cardiac, thoracic, and peripheral vascular surgery. Experience or training in heart/lung transplantation preferred. Initial contact should include curriculum vitae, clinical experience, and names of references.

Please respond to Box 162. 162G/J

Position available: thoracic and cardiovascular surgeon urgently needed for position with busy 2-man professional association at a large southwest medical center. Must be experienced in adult cardiac, pulmonary, esophageal, and vascular surgery. Must be board certified or eligible. Many benefits. Reply with curriculum vitae.

Please respond to Box 176. 176G

Additional cardiothoracic surgeon, BC/BE, to join expanding practice of cardiac/thoracic surgery at 500-bed affiliate of major medical center in Midwest. Skills in internal mammary grafting, valve repair, ventricular assist important, and familiarity with electrophysiological procedures desired. Excellent investigational facilities available with ample opportunity for clinical or basic science research. Private practice with academic affiliation—solid general surgery residency with active medical student participation. Salaried position leading to eventual partnership for the right individual. Send CV.

Please respond to Box 178. 178G/I

SITUATIONS WANTED

Cardiovascular and thoracic surgeon wishes to relocate. University trained with ABTS certification. Ten years' experience with extensive cardiac, thoracic, and peripheral vascular surgery. Would be interested in starting new program or association with group. Curriculum vitae and references available upon request.

Please respond to Box 117. 117C/H

Cardiovascular and thoracic surgeon, 37, ABS, ABTS, personable, strong technical skills and patient care, interested in joining group or starting new program.

Please respond to Box 133. 133E/H

Cardiovascular and thoracic surgeon wishes to relocate. ABS, ABTS with 10 years experience in adult cardiac, thoracic, and peripheral vascular surgery. All areas considered. Willing to initiate or help initiate new program.

Please respond to Box 136. 136E/H

Cardiovascular and thoracic surgeon, extensive experience, ABS, ABTS, university trained. CABG with IMA and vein, mitral valve reconstruction and valve replacement, extensive pulmonary and vascular experience including laser angioplasty. Solid research interest with 90 published papers. Wishes to join active cardiothoracic practice. Curriculum vitae and references on request.

Please respond to Box 138. 138E/G

Cardiothoracic surgeon, 36, wishes to relocate, preferably in Southeast or Midwest. ABS/ABTS. University and private group practice with extensive experience in complex adult thoracic and cardiovascular surgical disease. Interested in starting new program or associating with established practice.

Please respond to Box 177. 177G/I

Cardiovascular and thoracic surgeon, 42, American, ABS, ABTS, ABVS. Eight years private practice experience. Completed overseas fellowship in heart and heart/lung transplantation. Seeks opportunity with individual or group practice of cardiovascular and thoracic surgery. Curriculum vitae and references upon request.

Please respond to Box 199. 199G/I

FELLOWSHIPS

Fellowship in thoracic and cardiovascular surgery at Baylor University Medical Center.

Contact Dr Harold C. Urschel, 3600 Gaston Avenue, Suite 1201, Dallas, TX 75246; telephone (214) 824-2503. 129G/L

Physicians—Cardiothoracic fellowships available immediately; for cardiac center located on the north shore of Long Island with a busy program in adult and pediatric cardiac surgery. Opportunity for outstanding candidates at conclusion of fellowship to join full-time private practice associate group specializing in cardiac surgery. Applicants must have completed training in general surgery with special interest and/or training in cardiothoracic surgery. Salary commensurate with qualifications; excellent fringe benefits.

Resumes and references should be forwarded to Coordinator, Medical Staff Affairs, St. Francis Hospital, 100 Port Washington Blvd, Roslyn, NY 11576. An equal opportunity employer. 158F/H

Fellowship in cardiovascular surgery: Clinical training position in adult cardiovascular surgery with emphasis on use of the operating microscope for coronary bypass surgery available July 1989. Generous stipend and fringe benefits.

Please send curriculum vitae with requirements to John Bell-Thomson, MD, Chairman, Division of Cardiothoracic Surgery, Albert Einstein Medical Center, York & Tabor Roads, Philadelphia, PA 19141. 159FG

Vascular surgeon fellow: Deborah Heart & Lung Center is currently seeking qualified physician for fellowship training or surgical rotations in adult vascular surgery. Outstanding educational opportunities with excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart & Lung Center, Browns Mills, NJ 08015; (609) 893-6611, Ext 634. 175G/I

Surgical fellow—Clinical fellowship position available in adult and pediatric cardiothoracic surgery. Large volume of cases. NJ license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Department of Surgery, Deborah Heart & Lung Center, Browns Mills, NJ 08015. 167G/L

Pediatric cardiovascular fellowship position available 7/89 for board credit at Children's Hospital of New Jersey for 4 months. Must have New Jersey license.

Contact Joseph J. Amato, MD, Director, Department of Pediatric Cardiovascular Surgery, Children's Hospital of New Jersey (UHMC), 15 South Ninth St, Newark, NJ 07107; (201) 268-8606. 179GH

SURGERY UPDATE

SEPTEMBER 22-23, 1989

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6580 FANNIN
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For Further Information Contact:
Rafael Espada, M.D.
Program Director
(713) 798-4556

Carol J. Soroka
Program Coordinator
The Office of Continuing Education
Baylor College of Medicine
Houston, Texas 77030
(713) 798-6020

This year's "Surgery Update" meeting will present current concepts and techniques in general, pediatric, abdominal, hepatic and cardiovascular surgery.

Presentations will cover such topics as:

- Unusual manifestations of abdominal aortic aneurysms
- Transplantation of the pancreas
- Hepatic surgery
- Mesenteric ischemia
- Surgical treatment of biliary tract disease
- Current concepts in atherosclerosis
- Current concepts in the treatment of colon cancer
- Current concepts in the treatment of breast cancer
- Update in pediatric surgery

FACULTY

Charles M. Balch, M.D.
Jon M. Burch, M.D.
E. Stanley Crawford, M.D.
Michael E. DeBakey, M.D.
Rafael Espada, M.D.
Peter B. Fisher, M.D.
Michael W.L. Gauderer, M.D.
Franklin J. Harberg, M.D.

David C. Hohn, M.D.
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Montague Lane, M.D.
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Ernest Max, M.D.
Charles McCollum, M.D.
George Noon, M.D.

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Mark Roh, M.D.
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Fernando Stein, M.D.
David Vanderpool, M.D.
Hartwell Whisennand, M.

CURRENT CONTROVERSIES AND TECHNIQUES IN CONGENITAL HEART SURGERY

Baltimore Inner Harbor
Baltimore, Maryland

SEPTEMBER 8-9, 1989

Division of Cardiac Surgery University of Nebraska

Immediately prior to the annual meeting of the Society of Thoracic Surgeons in Baltimore, Maryland which begins September 10, 1989

Topics:

Fetal Diagnosis and Surgery
Arterial Switch — Tricks and Problems
Hypoplastic Left Heart — Norwood vs Transplant
Pulmonary Atresia
  Intact Septum — Sinusoids
  VSD — Unifocalization
Cavo Pulmonary Connections
Heart-Lung Transplant
Small Aortic Root
Hypoplastic Isthmus
Coarctation of Aorta

GUEST FACULTY

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John Brown
Aldo Castaneda
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Richard Jonas
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Roger Mee
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Bruno Messner
William Norwood
Helmut Oerlurt
Albert Pacifico
Francisco Puga
Glenn Pennington
Jan Quagebeur
Jaroslav Stark
Edward Verrier
William G. Williams
Magdi Yacoub
and others

For further information, complete, detach and mail this form to Ms. Terry Young,
11 S. Paca Street, University Square Bldg., Suite 304, Baltimore, Maryland 21201

Please send information on
CURRENT CONTROVERSIES AND TECHNIQUES IN
CONGENITAL HEART SURGERY
to:

Name:
Address:
Phone:
Specialty:

FELLOWSHIP IN THORACIC SURGERY

The Surgery Branch of the National Cancer Institute, National Institutes of Health has an immediate opening for a Fellowship in Thoracic Surgery. This program offers a broad experience in thoracic oncologic surgery with opportunities to participate in clinical and basic research. A two-year program is available for candidates desiring additional research experience. Applicants must be Board Eligible in Thoracic Surgery. Please submit a current curriculum vitae and bibliography. Salary for this Fellowship position is dependent on background and qualifications.

CONTACT:
Harvey T. Pass, M.D.
Head, Thoracic Oncology Section
Surgery Branch
National Cancer Institute
Bldg. 10, Room 2B07
9000 Rockville Pike
Bethesda, Maryland 20892
(301) 496-2127

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PROFESSOR AND HEAD SECTION OF CARDIOVASCULAR-THORACIC SURGERY

Applications are invited for the position of Head of the Section of CVT Surgery, Department of Surgery at the Faculty of Medicine, University of Manitoba for a five year term commencing July 1, 1990, or as soon thereafter as possible.

Candidates should have a substantial record of academic achievement in CVT Surgery and extensive experience in teaching and research, as well as proven administrative experience. The Section is responsible for programs of education at the undergraduate and graduate levels.

Candidates must have Senior Specialty qualifications in Surgery in the country of current practice and must be eligible for registration with the College of Physicians and Surgeons of Manitoba in their particular specialty.

The University of Manitoba offers good working conditions, a competitive salary and an attractive fringe benefit package.

Both men and women are encouraged to apply. In accordance with Canadian Immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada.

Applications and nominations should be accompanied by a curriculum vitae and submitted not later than September 20, 1989 to:

Dr. N.R. Anthonisen, Chair
Section of CVT Search Committee
Faculty of Medicine, University of Manitoba
A101-753 McDermot Avenue
Winnipeg, Manitoba, Canada R3E 0W3

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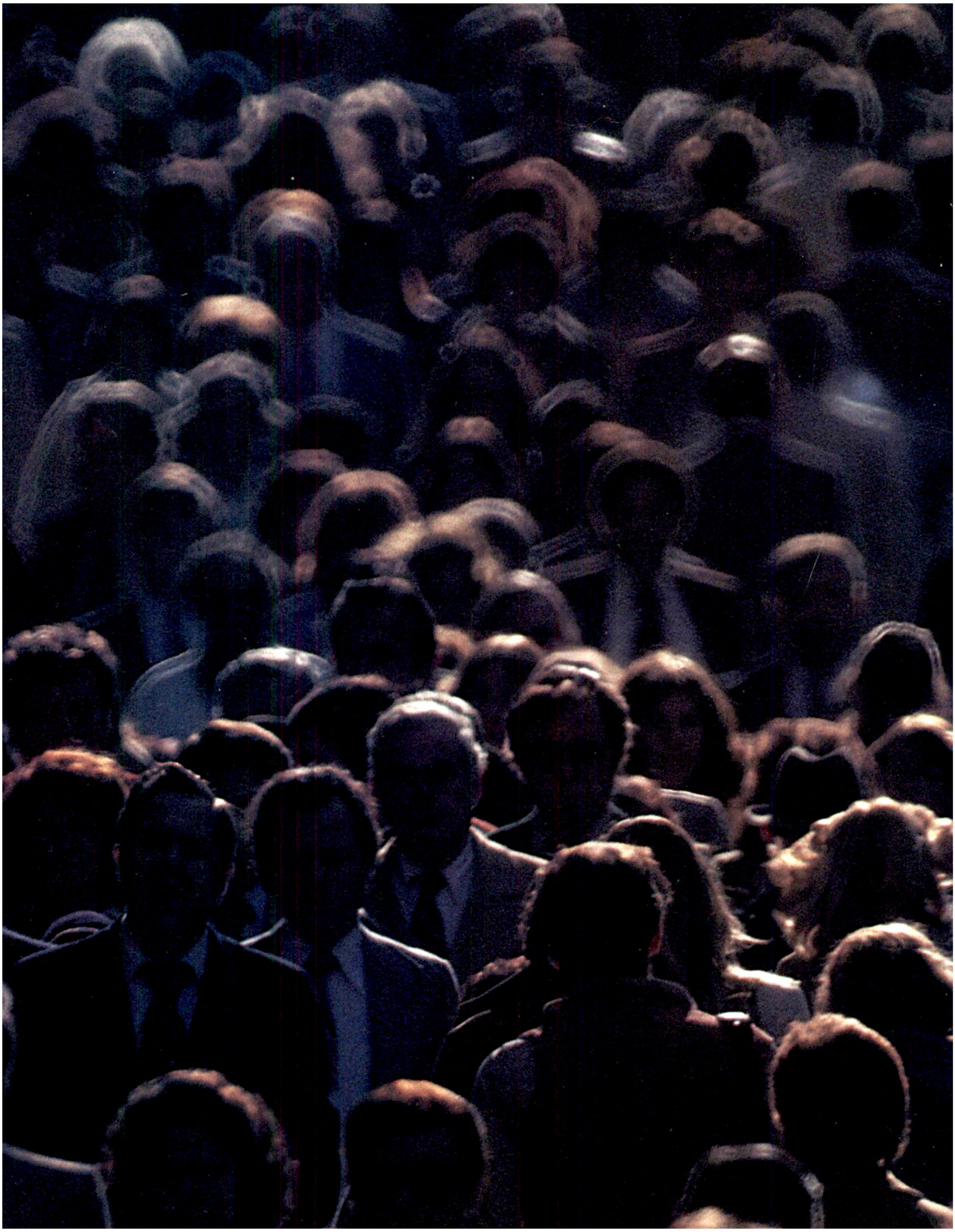

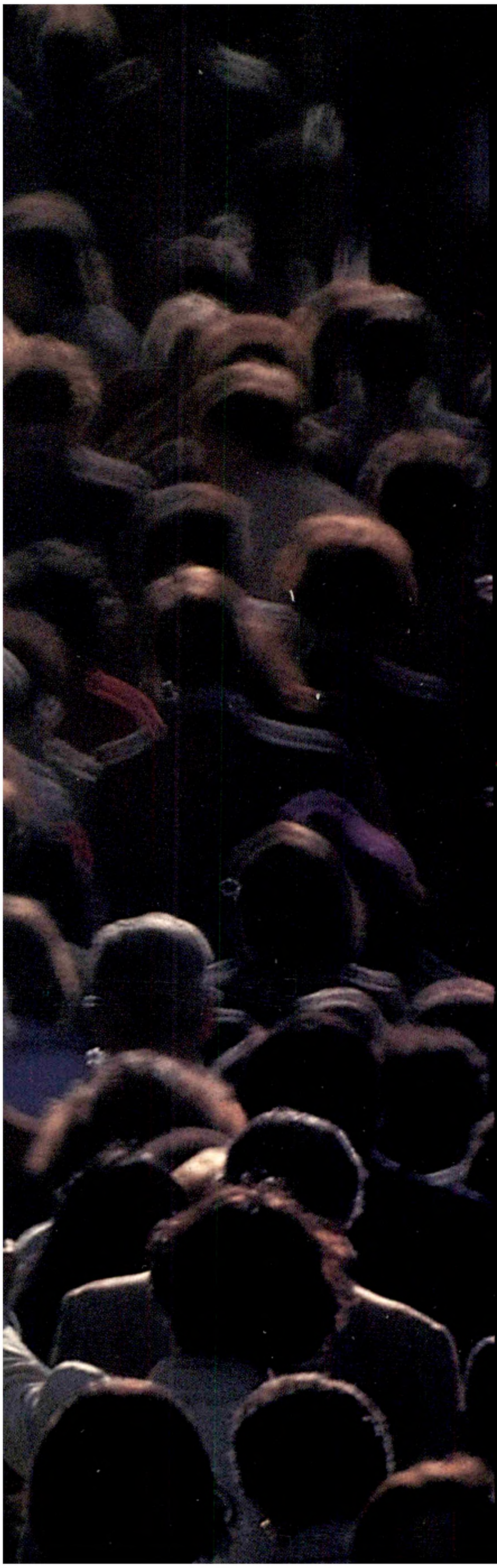

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VOLUME 48 NUMBER 2 AUGUST 1989 ISSN 0003-4975

THE ANNALS OF THORACIC SURGERY

Official Journal of The Society of Thoracic Surgeons and the Southern Thoracic Surgical Association

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Twenty-fifth Anniversary Meeting of The Society of Thoracic Surgeons
September 11–13, 1989, Baltimore Convention Center, Baltimore, MD

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association
November 9–11, 1989, Phoenician Golf and Tennis Resort, Scottsdale, AZ

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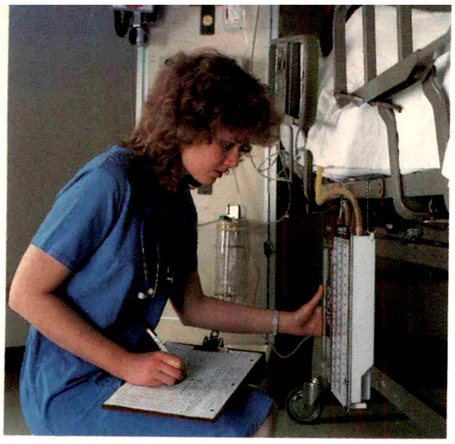

"My job is
to give each
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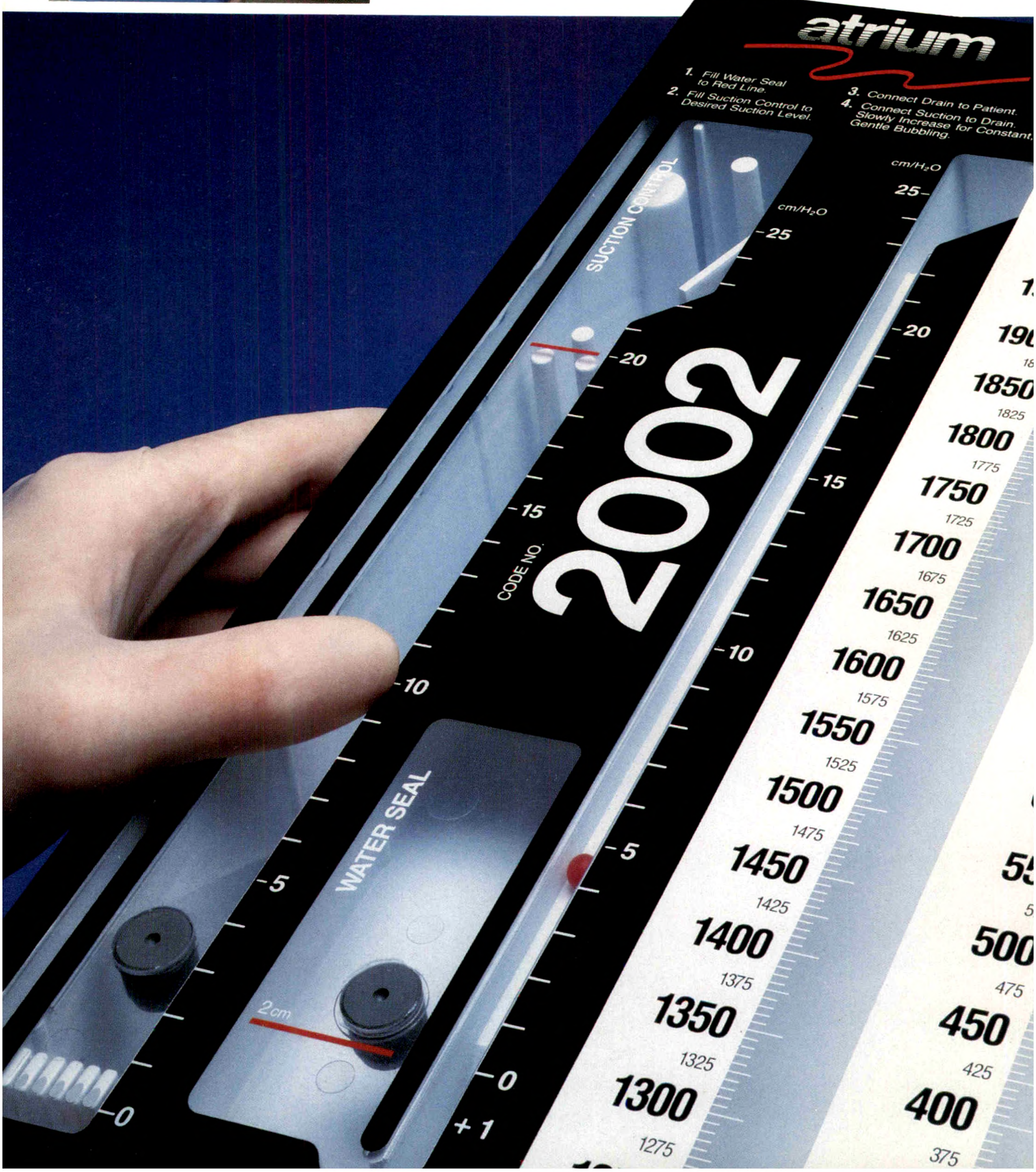
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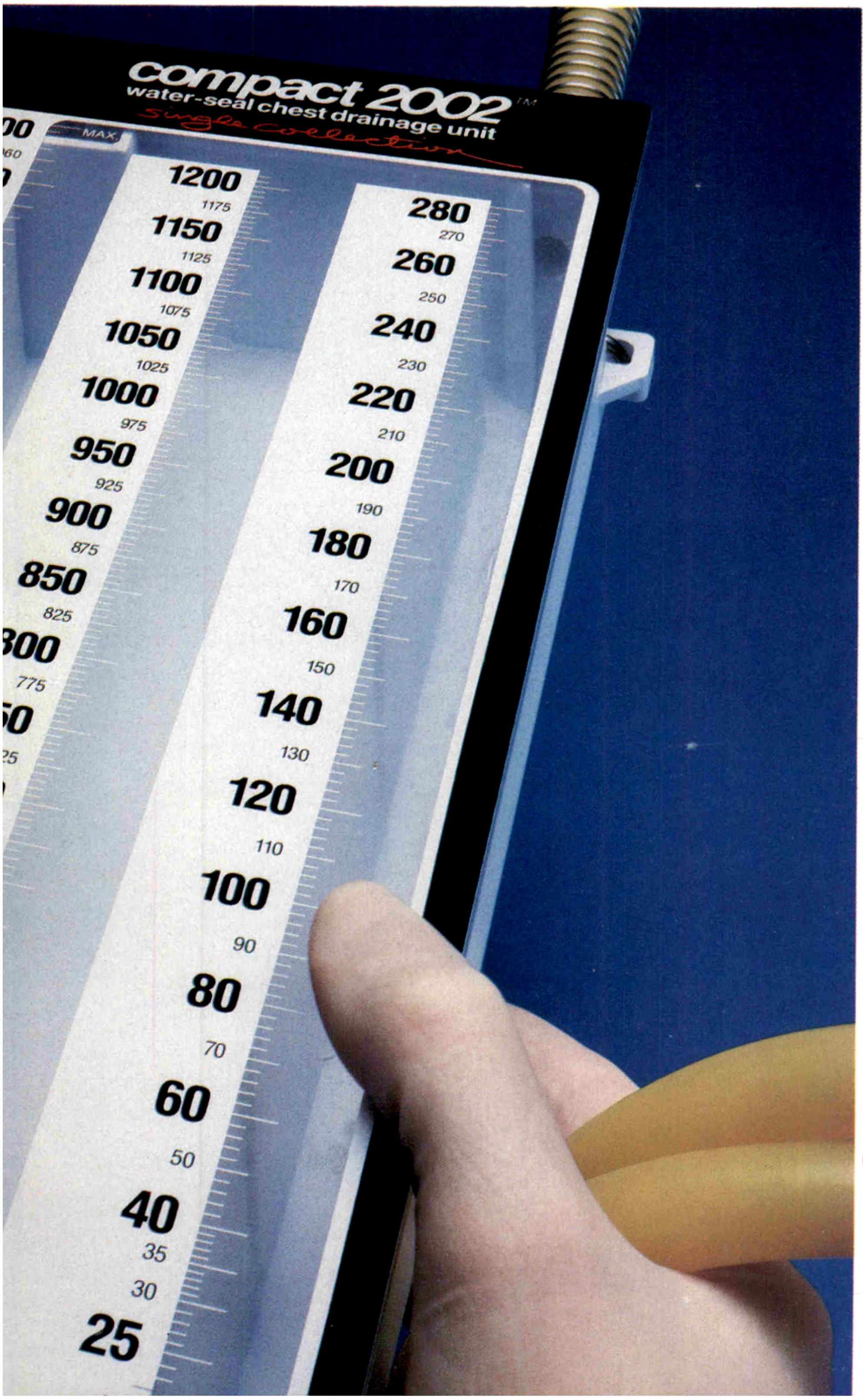

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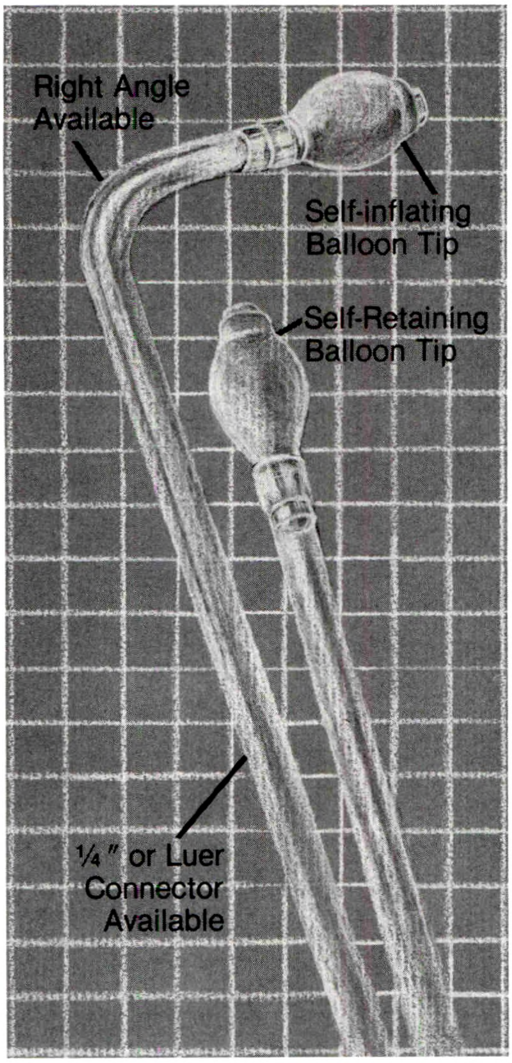

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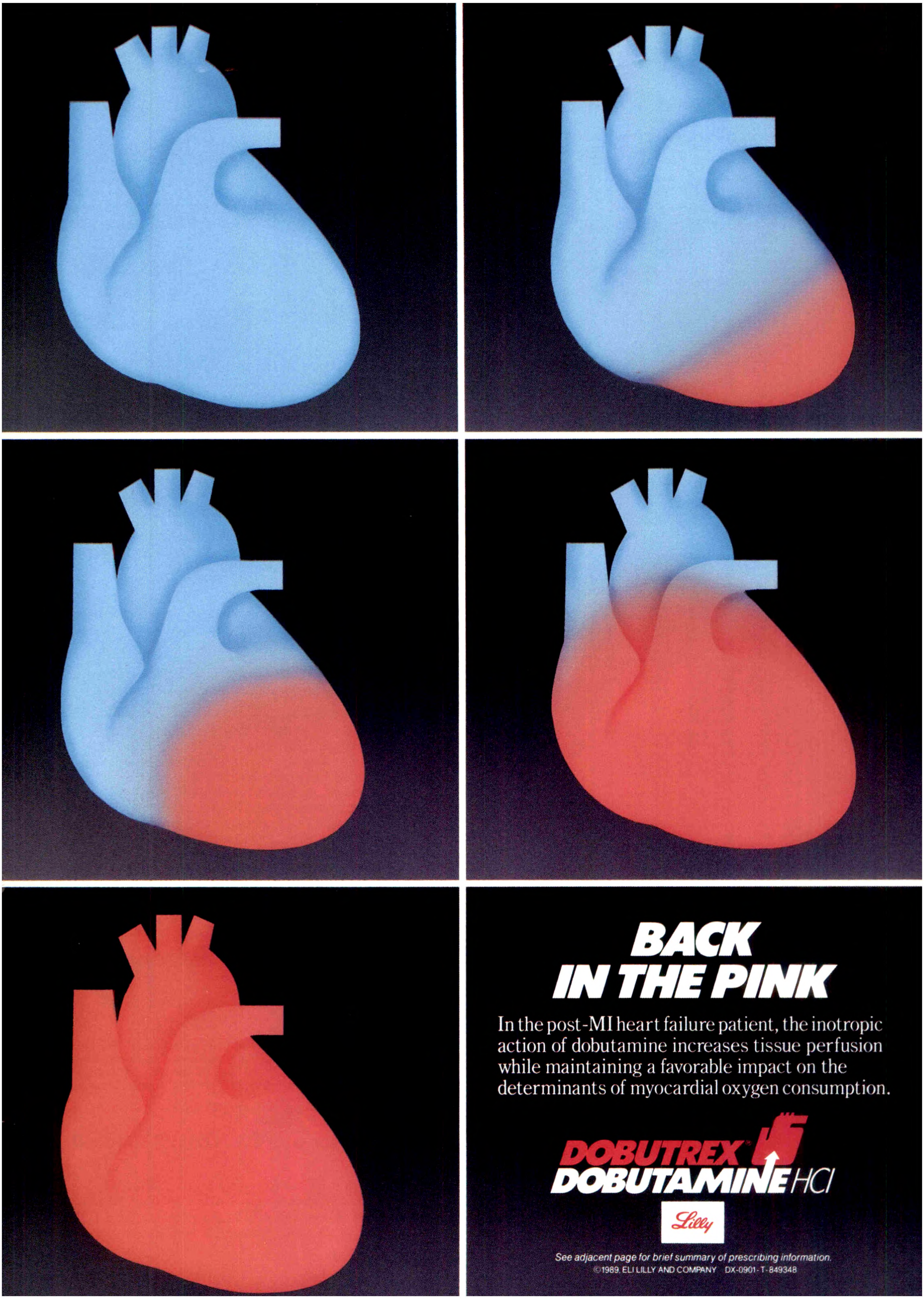

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In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short term—not more than several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas output returned toward baseline values in others.

The onset of action of Dobutrex Solution is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

Indications and Usage: Dobutrex Solution is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex Solution.

Contraindications: Dobutrex Solution is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to Dobutrex Solution.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex Solution may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Usually, reduction of dosage reverses these effects. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex Solution may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

3. *Hypersensitivity*—Reactions suggestive of hypersensitivity associated with administration of Dobutrex Solution, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

4. Dobutrex Solution contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Precautions: 1. During the administration of Dobutrex Solution, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex Solution.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex Solution is instituted.

3. Animal studies indicate that dobutamine may be ineffective if the patient has recently received a ß-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex Solution following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent that increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex Solution for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex Solution was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10- to 20-mm increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients. (*See* Warnings *regarding exaggerated chronotropic and pressor effects.*) Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Hypotension—Precipitous decreases in blood pressure have occasionally been described in association wth dobutamine therapy. Decreasing the dose or discontinuing the infusion typically results in rapid return of blood pressure to baseline values.

Reactions at Sites of Intravenous Infusion—Phlebitis has occasionally been reported. Local inflammatory changes have been described following inadvertent infiltration.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1% to 3% of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex Solution have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

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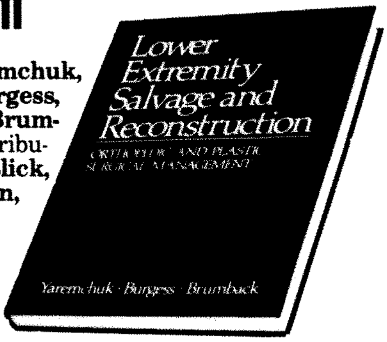
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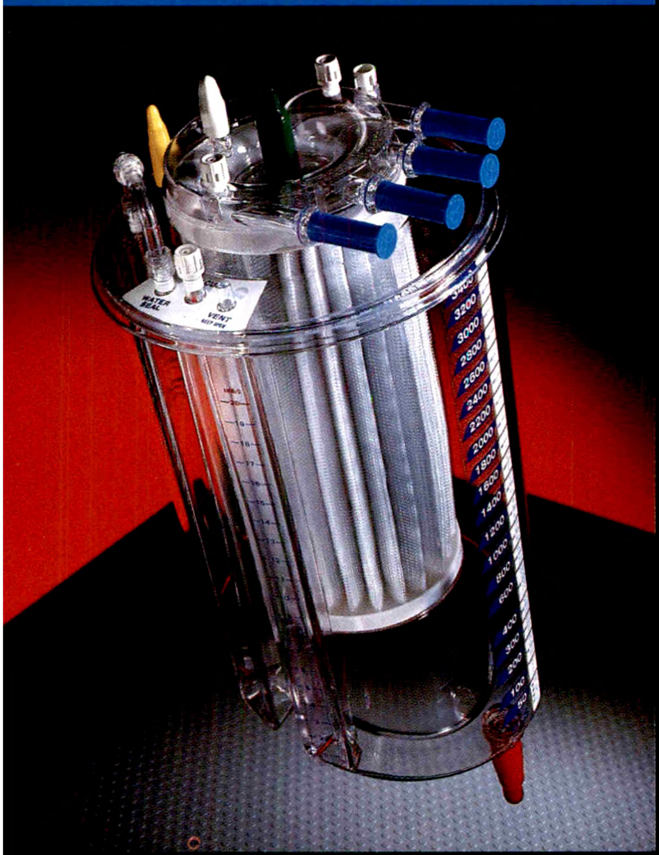

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8. Diehl JT, Eichhorn EJ, Konstam MA, et al. Efficacy of retrograde coronary sinus cardioplegia in patients undergoing myocardial revascularization: a prospective randomized trial. Ann Thorac Surg 1988;45:595–602.

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Chapter in Book

12. Katz PO. Achalasia. In: Castell DO, Richter JE, Dalton CB, eds. Esophageal motility testing. New York: Elsevier Science Publishing Company, 1987:107.

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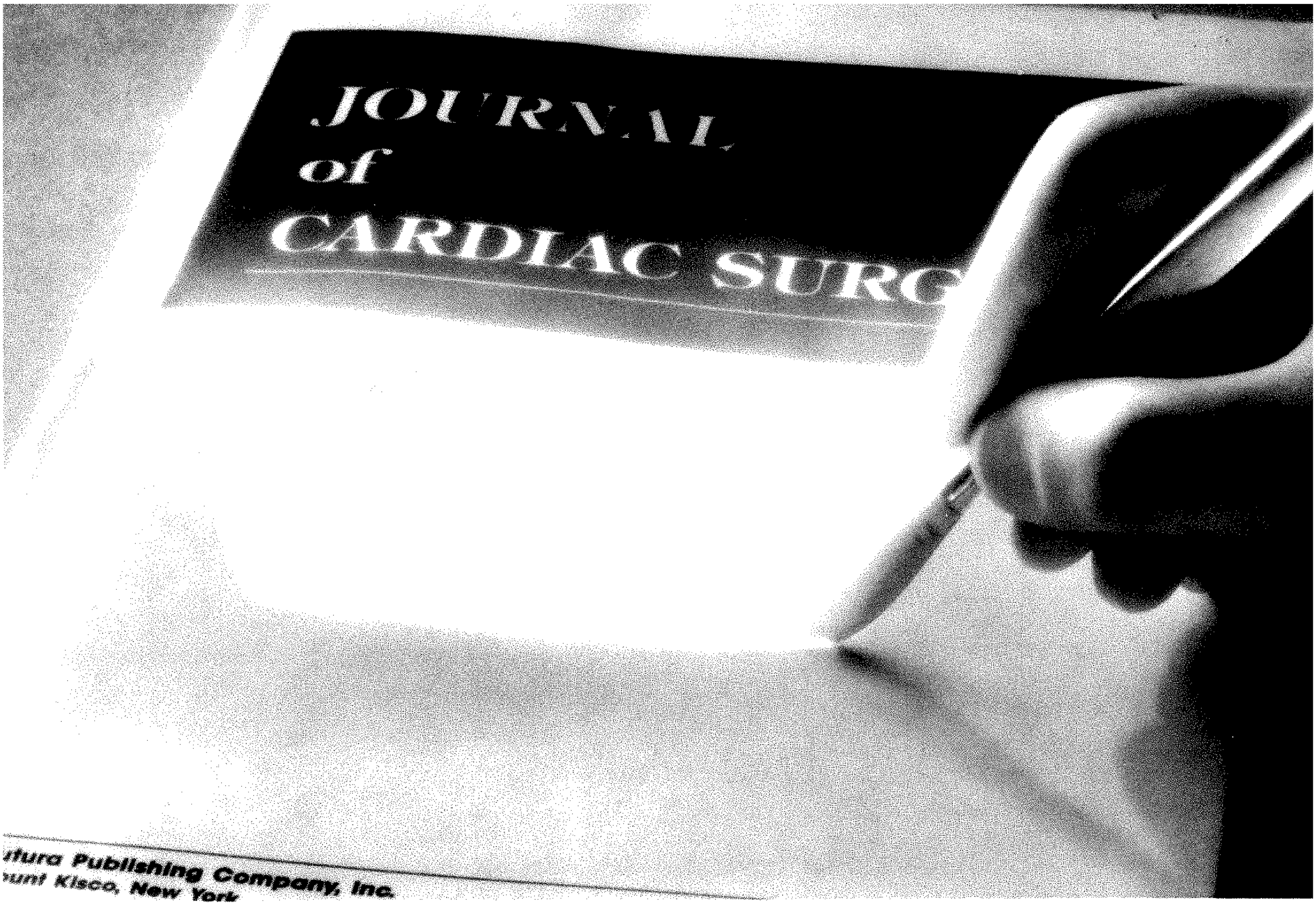

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WARNING

It is recommended that Blenoxane be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Pulmonary fibrosis is the most severe toxicity associated with Blenoxane. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with Blenoxane.

DESCRIPTION

Blenoxane (sterile bleomycin sulfate, USP) is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of **Streptomyces verticillus.** It is freely soluble in water.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.

ACTION

Although the exact mechanism of action of Blenoxane is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

In mice, high concentrations of Blenoxane are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have been found to have high concentrations of Blenoxane in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of Blenoxane found in bone marrow may be related to high levels of Blenoxane degradative enzymes found in that tissue.

In patients with a creatinine clearance of >35 mL per minute, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of <35 mL per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. In humans, 60% to 70% of an administered dose is recovered in the urine as active bleomycin.

INDICATIONS

Blenoxane should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:

Squamous Cell Carcinoma–Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingiva, epiglottis, larynx), skin, penis, cervix, and vulva. The response to Blenoxane is poorer in patients with head and neck cancer previously irradiated.

Lymphomas–Hodgkin's, reticulum cell sarcoma, lymphosarcoma.

Testicular Carcinoma–Embryonal cell, choriocarcinoma, and teratocarcinoma.

CONTRAINDICATIONS

Blenoxane is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

WARNINGS

Patients receiving Blenoxane must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by Blenoxane progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended.

Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of lymphoma patients treated with Blenoxane. Since these usually occur after the first or second dose, careful monitoring is essential after these doses.

Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Usage in Pregnancy: Safe use of Blenoxane in pregnant women has not been established.

ADVERSE REACTIONS

Pulmonary–This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to Blenoxane has been extremely difficult. The earliest symptom associated with Blenoxane pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, Blenoxane-induced pneumonitis produces nonspecific patchy opacities, usually of the lower lung fields. The most common changes in pulmonary function tests are a decrease in total lung volume and a decrease in vital capacity. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to Blenoxane toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific, eg, similar changes are seen in radiation pneumonitis, pneumocystic pneumonitis.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1 to 2 weeks. If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Recent studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{CO}) during treatment with Blenoxane may be an indicator of subclinical pulmonary toxicity. It is recommended that the DL_{CO} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DL_{CO} falls below 30% to 35% of the pretreatment value.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations than usually would be considered safe. Suggested preventive measures are:

(1) Maintain FI O_2 at concentrations approximating that of room air (25%) during surgery and the postoperative period.
(2) Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during Blenoxane infusions. Although each patient must be individually evaluated, further courses of Blenoxane do not appear to be contraindicated.

Idiosyncratic Reactions–In approximately 1% of the lymphoma patients treated with Blenoxane, an idiosyncratic reaction, similar to anaphylaxis clinically, has been reported. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose. It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic including volume expansion, pressor agents, antihistamines, and corticosteroids.

Integument and Mucous Membranes–These are the most frequent side effects being reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue Blenoxane therapy in 2% of treated patients because of these toxicities.

Skin toxicity is a relatively late manifestation usually developing in the 2nd and 3rd week of treatment after 150 to 200 units of Blenoxane have been administered and appears to be related to the cumulative dose.

Other–Vascular toxicities coincident with the use of Blenoxane in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with Blenoxane in combination with vinblastine with or without cisplatin or, in a few cases, with Blenoxane as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, Blenoxane, vinblastine, hypomagnesemia, or a combination of any of these factors.

Fever, chills, and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions were reported infrequently.

DOSAGE

Because of the possibility of an anaphylactoid reaction, lymphoma patients should be treated with 2 units or less for the first two doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedule is recommended: **Squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, testicular carcinoma**–0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease–0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

Pulmonary toxicity of Blenoxane appears to be dose related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Note: When Blenoxane is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's Disease and testicular tumors is prompt and noted within 2 weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as 3 weeks before any improvement is noted.

ADMINISTRATION

Blenoxane may be given by the intramuscular, intravenous, or subcutaneous routes.

Intramuscular or Subcutaneous–Dissolve the contents of a Blenoxane vial in 1 to 5 mL of Sterile Water for Injection, USP, Sodium Chloride for Injection, USP, 5% Dextrose Injection, USP, or Bacteriostatic Water for Injection, USP.

Intravenous–Dissolve the contents of the vial in 5 mL or more of a solution suitable for injection, eg, physiologic saline or glucose, and administer slowly over a period of 10 minutes.

STABILITY

The sterile powder is stable under refrigeration (2°-8°C) and should not be used after the expiration date is reached.

Blenoxane is stable for 24 hours at room temperature in Sodium Chloride or 5% Dextrose Solution.

Blenoxane is stable for 24 hours in 5% Dextrose containing heparin 100 units per mL or 1000 units per mL.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

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7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. Am J Hosp Pharm 1986; 43: 1193-1204.

SUPPLY

Each vial contains 15 units of Blenoxane as sterile bleomycin sulfate, USP

NDC 0015-3010-20

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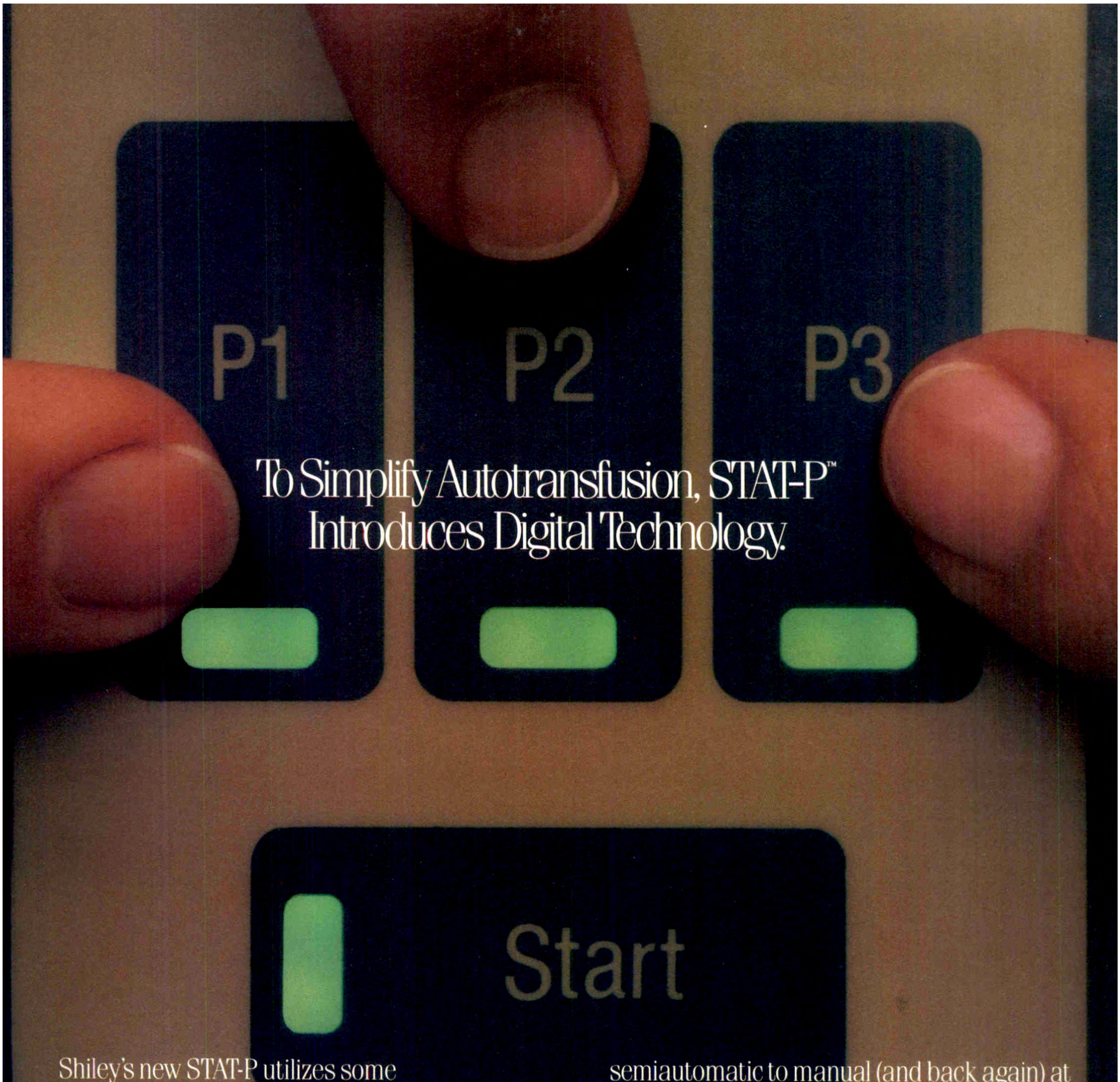

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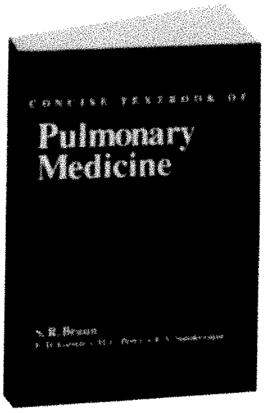

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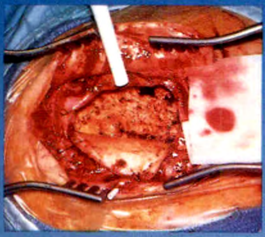

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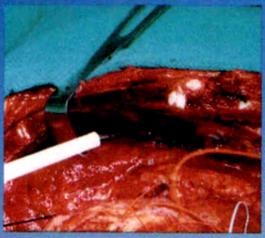

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2. Remove the Tyvek† blister lid from the inner tray to expose the sterile contents.
3. Using the sterile syringe equipped with the needle, draw the desired amount of saline diluent from the vial into the syringe.
4. Inject the saline diluent into the THROMBOGEN* vial from the syringe to reconstitute the THROMBOGEN* powder.
5. When the THROMBOGEN* is completely dissolved, draw the THROMBOGEN* solution into the syringe.
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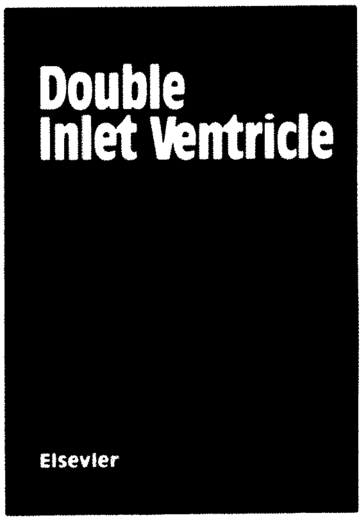

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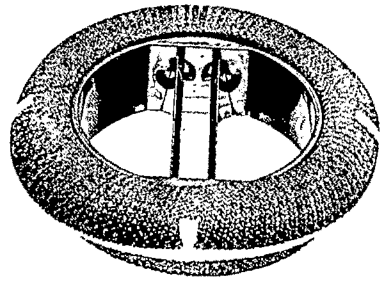

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Should Surgical Support Within the Same Institution Be Required for Percutaneous Transluminal Coronary Angioplasty?

Lawrence I. Bonchek, MD

Department of Surgery, Lancaster General Hospital, Lancaster, Pennsylvania

Guidelines for percutaneous transluminal coronary angioplasty (PTCA) were recently reported by the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures [1]. The need for surgical backup was summarized with the statement that "an experienced cardiovascular surgical team should be available *within the institution* for emergency surgery for all angioplasty procedures" [emphasis added]. Further, the report expressed the subcommittee's strong feeling that "there should be no exception to this requirement . . . and . . . all arrangements requiring the transportation of patients to off-site surgical facilities for such emergency surgery fail to meet the necessary standards of care . . . and cannot be condoned."

Although this stipulation seems attractive at first, its effects may not be entirely desirable. The restriction is presumably intended to discourage angioplasty not only in free-standing catheterization laboratories, but even in hospital-based catheterization laboratories, if those hospitals do not have cardiac surgery programs. A more likely outcome, however, is the proliferation of cardiac surgery programs to support every hospital catheterization laboratory that does not wish to be excluded from the performance of angioplasty. According to the 1987 summary of facilities and services in the United States, there were at least 1,234 cardiac catheterization laboratories (19.6% of 6,281 hospitals reporting) and 793 open heart surgery facilities (12.6% of hospitals reporting) [2]. As it seems reasonable to assume that every hospital with open heart surgery capability also has a catheterization laboratory, there remain a minimum of 441 catheterization laboratories unsupported by open heart surgery, but with potential interest in developing an open heart surgery program—if only to support PTCA. Proliferation of cardiac surgery programs will decrease the number of cases done in each existing program, and could lead to the undesirable establishment of large numbers of programs that carry out an inadequate number of cases [3]. That this phenomenon is already occurring can be seen in the advertisements for heart surgeons placed in major cardiology and cardiac surgery journals, extolling the advantages of living in smaller communities and predicting initial open heart surgery caseloads of 100 to 150 cases per year. Additionally, these new low-volume programs will have the incentive to do nonessential operations to maintain their inadequate caseloads. The Task Force report will only accelerate this trend toward the establishment of cardiac surgery programs whose major purpose is the support and legitimization of PTCA programs.

The presumption that it is unacceptable to perform PTCA in a hospital that lacks cardiac surgery can be debated. Interdiction of such a practice fails to take into account the realities of surgical standby as it is provided in busy, frontline, community hospitals, where so much cardiac surgery is done in the United States today. It is a fact that even when an operating room is "available" it is unlikely that a full cadre of operating room nurses and—more importantly—an anesthesiologist will be idly standing by and instantly ready, even if there is an available cardiac surgeon. (Indeed, appropriate reimbursement for standby of a full, "combat-ready" team could become prohibitive [4].)

Moreover, in large institutions, transportation of the patient from the catheterization laboratory to the operating room (often on another floor) may consume 5 to 10 or more minutes on a stretcher. It is therefore particularly relevant that the Task Force's requirement that cardiac surgery be available "within the institution" was elaborated by a footnote to include "those instances in which two adjacent hospitals are physically connected such that emergency transport by stretcher or gurney can be achieved rapidly and effectively" [1]. Presumably, it would therefore be acceptable to transport a patient on a stretcher down (or up) one elevator, through a connecting tunnel or elevated walkway, up (or down) another elevator, all the while accompanied perhaps by a balloon pump console, several battery-operated intravenous transfusion regulators, and a ventilation support system. It strains credibility to suppose that compared with such a journey, a greater increment of risk is imposed by travel for 5 to 15 minutes between hospitals that may be less than 2 miles apart in the controlled environment of a mobile intensive care unit, with its supporting equipment and personnel.

The interval required for the trip need not be a critical factor in the context of circumstances that usually surround emergency coronary bypass for PTCA failure. There is usually a considerable interval between the first suspicion that an angioplasty may have an adverse outcome and the final decision to proceed with operation after a variety of "bail-out" maneuvers have been tried. During this interval, final preparation of the operating room and assembly of personnel can take place, as it would in any institution. In my own experience, a slightly

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longer interval to revascularization has seemed much less important in determining the extent of myocardial injury after failed PTCA than has the presence or absence of residual patency in the offending coronary artery, because it is the residual coronary lumen that regulates perfusion of the jeopardized myocardium. Furthermore, if in-house surgical backup is provided on a "next room available" basis [5] (a practice tacitly condoned by the Task Force report), the delay before revascularization begins may be even longer than the time required for an ambulance ride to an operating room that is vacant and immediately available.

It is therefore unfortunate that the Task Force left no opportunity for closely cooperating institutions to develop plans that would allow PTCA in one institution to be supported by a cardiac surgery program in another that is geographically separate but in close proximity. In contrast, the German Society for Cardiology has recognized these realities in its policy statement about surgical backup for PTCA [6].

> Elective balloon dilatations may only be performed after agreement with and temporary coordination with a cardiac surgical center . . . . as an acute occlusion of a coronary artery must be anticipated in a certain percentage of balloon dilatations. . . . The interval between the occurrence of irreversible coronary occlusion and operative revascularization should be as short as possible. This applies in particular to the time of transport and the route to the operative theater. During transport, the capacity to perform life-saving measures (resuscitation, intubation, ventilation, treatment of shock) must be available. The necessary organizational measures must be agreed upon in advance.

This policy statement carefully avoids rigid proscriptions, and permits some flexibility in developing cooperative arrangements, while emphasizing the importance of rapid revascularization.

There are circumstances in the United States where hospitals are literally across the street from each other, but remain administratively and structurally separate. Must both institutions have cardiac surgery programs to support separate catheterization laboratories? Is it realistic to expect a major institution to close its catheterization laboratory, with the inevitable loss of hospital prestige and revenue, as well as the loss of invasive cardiologists who will move to the competing institution? Such an outward migration could also adversely affect the general quality of medical care at the institutions that are left behind. No competitive institution will be content with such a course. Instead, in the current climate of weak certificate-of-need regulations, another unneeded cardiac surgery program will be started.

It is relevant to note that in 1982, when guidelines for PTCA were promulgated by the Executive Committee of the National Heart, Lung, and Blood Institute PTCA Registry [7], only the "immediate availability" of a surgical team was recommended. Yet now, when PTCA complication rates for comparable cases are lower than they were in 1982, and fewer than 5% of patients require an emergency operation for failed PTCA, in-house surgical backup is being mandated.

It is not far-fetched to suggest that the proliferation of low volume (and, by inference, higher mortality) cardiac surgery programs whose primary purpose is to legitimize their associated PTCA laboratories will cause the loss of more myocardium (and perhaps even lives) than will be saved by the new requirement for surgical support within the same institution.

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The Olden Days of Surgery for Tuberculosis

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Those people who talk about "the good old days" either were not there or have very imperfect memories. Three generations ago, tuberculosis was the seventh leading cause of death in the United States and a leading cause of death in the age group of 15 to 44 years [1]. Many of us were introduced to thoracic surgery through illnesses that are relatively uncommon today: bronchiectasis, lung abscess, and tuberculosis.

If we go back in history, surgeons have been involved in the treatment of tuberculosis for a hundred years, even before the invention of the roentgenograph in 1895 [2]. In 1891, Tuffier did a successful wedge resection of the apex of an upper lobe. John B. Murphy, "the Stormy Petrel of Chicago Surgery," introduced artificial pneumothorax to the United States only 4 years after Carlo Forlanini published his first series from Pavia. Collapse therapy by thoracoplasty was the preferred surgical treatment for patients who failed to respond to rest and artificial pneumothorax, from the turn of the century until after World War II. In the days before streptomycin (1945), paraminosalicylic acid (1946), and isoniazide (1951), lobectomy and pneumonectomy were reserved for desperate situations— "salvage patients." The risk of resection was high; in four major series published in 1946 through 1947, the average mortality was 28%. The leading causes of death were bronchopleural fistula with consequent empyema and exacerbation and spread of tuberculosis [2].

The picture changed dramatically after introduction of effective antibiotic treatment of pulmonary tuberculosis. Our team at the St. Albans, NY, Naval Hospital performed 150 consecutive segmental resections and lobectomies from 1952 to 1954 with no deaths; this was a very favorable group of young men and women who happened to have tuberculosis. In 1956, John Steele could report 1,554 cases of segmental resections done in Veterans Administrations hospitals with 1% mortality [3]. A series of 30 consecutive pneumonectomies done between 1959 and 1968 at the National Jewish Hospital in Denver resulted in 1 postoperative death (in a chronically psychotic, intractable patient).

The report in this issue by Reed, Parker, and Crawford [4] of resections in 24 patients with no deaths is an excellent example of what can be accomplished by skilled surgeons treating relatively poor risk patients. Their indications for resection were severe bleeding in 14 patients, drug-resistant tubercle bacilli or atypical mycobacteria in 5, possible neoplasm in 3, bronchiectasis in 2.

It is interesting to hark back to 1957, to indications for resection at the University of Michigan, as given by Sloan and Milnes [5]:

1. Open cavity after 3 to 6 months of adequate antituberculosis drug therapy, with or without positive sputum.
2. Residual caseous nodules ("necrotic residuals") more than 2 cm in diameter.
3. "Unanticipated slow resolution of disease under presumed adequate antimicrobial therapy."
4. Diffuse nodular disease.
5. Chronic fibroid disease with positive sputum.
6. Atelectasis of a segment or a lobe.
7. Bronchial stenosis with distal disease.
8. Bronchiectasis with positive sputum or symptoms.
9. Destroyed pulmonary segment, lobe, or lung.
10. Failed thoracoplasty.
11. Suspected neoplasm.

Today, we know more about the natural history of tuberculosis after effective antibiotic therapy. We no longer operate on patients for asymptomatic shadows. Contrary to our older notions, the open-healed cavity is no longer considered a threat, unless a fungus ball develops. Asymptomatic bronchiectasis or scarred lung tissue need not be resected unless the patient develops bleeding or repeated episodes of pneumonitis. A bronchopleural fistula with chronic empyema may be benefited by a pleuropneumonectomy. However, even in such situations one can often control the problem with an Eloesser flap for chronic open drainage, and later the space can be obliterated with a pedicled muscle graft. Unfortunately, most of the serious problems we see today are in patients who have relapsed after one or more courses of antimicrobial therapy.

One of my teachers, George Gomori, once said: "Everyone would like Nature to be black and white with sharp outlines, but frequently Nature is gray with fuzzy borders." There are still some gray, fuzzy areas in the surgical treatment of pulmonary tuberculosis: (1) Can we improve the balance between the patient's immune system and his or her infection by "debulking" the disease? I think this may be true for *Mycobacterium kansasii* or *Mycobacterium avium-intracellulare* and for the patient with relapse-retreatment *Mycobacterium tuberculosis*, where we have limited antibiotic efficacy. (2) How far should we risk pulmonary insufficiency or crippling in the elderly, "good chronic" patient who has no serious symptoms and only an occasional weakly positive sputum culture? My goal is maximizing comfort and longevity without stamping out

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every last mycobacterium. (3) Is there still a group of patients with limited pulmonary function for whom a lesser operation, like plombage, might be more appropriate?

Antibiotics are the primary weapons against infections, including tuberculosis. Reed, Parker, and Crawford have focused our attention on an important group of patients who have serious mechanical problems that persist after antimicrobial treatment. Probably fewer than 5% of patients will have such life-threatening problems after modern antimicrobial therapy for 9 to 12 months, and it is in this select group that pulmonary resection can make a safe, effective contribution.

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Hazards of Transthoracic Needle Biopsy of the Lung

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Despite the widespread employment of transthoracic needle aspiration biopsy of the lung, thoracic surgeons and pulmonologists remain concerned about the frequency and degree of seriousness of the various complications of this valuable diagnostic tool. Pneumothorax occurs in 25% of biopsies, but this is easily recognized and managed. The mortality of the procedure is probably less than 0.1%, with no deaths at all reported in most series, large or small. Lalli and associates [1] reported two deaths in 1,296 biopsies, one of which was a suicide! Deaths are usually due to air embolism, either venous or arterial [2]. Undoubtedly there have been unreported deaths.

Implantation of tumor along the needle track is extremely rare with the use of the standard thin needles. The report by Seyfer and colleagues [3] in this issue is the fourth well-documented case [4–6] of needle track implantation in the lung or chest wall after thin-needle biopsy. Even if we assume that there are probably some unreported cases, the frequency of this complication is clearly very low.

Animal experiments cited by Seyfer and associates show a high incidence of malignant cells in the needle track after biopsy. Why then is the appearance of postbiopsy chest wall metastases so rare in humans? A partial explanation may lie in the fact that, in the past, the majority of needle aspirations for malignant tumors were carried out to confirm the diagnosis in cases that were clearly inoperable. Many of these patients were then given radiation therapy, which probably sterilized microscopic implants, and others with advanced disease presumably died of systemic tumor metastases before tumor implants from the needle biopsy had time to become clinically apparent. In most cases, it would appear that the tumor cells in the needle track fail to form metastatic deposits.

Such hazards, although real, must be considered in the context of the advantages of performing the biopsy. As many solitary nodules are benign, needle biopsy offers a reasonable chance of establishing benignity so that exploratory thoracotomy, with its small but definite mortality, may be obviated. These competing risks can be compared more accurately by including the likelihood of benignity and the ability of the needle biopsy to reliably define benign lesions in the decision process.

In an analysis of the optimal management of solitary pulmonary nodules [7], the strategy of immediate thoracotomy was compared with the strategy of initial needle biopsy, expressed in terms of average years of life expectancy. Immediate thoracotomy for solitary uncalcified pulmonary nodules of unknown stability conferred a slightly greater average life expectancy than the biopsy strategy if the projected probability that the nodule was malignant was greater than 70%, whereas the strategy of initial needle biopsy was marginally preferable to immediate thoracotomy if the probability that the nodule was malignant was less than 70%. The clinical variables employed in the calculation of the probability of malignancy in a nodule included the age of the patient, the smoking history, and nodule diameter [8].

As would be expected, the advantage for needle biopsy as the preliminary procedure becomes somewhat greater if the predicted surgical mortality for exploratory thoracotomy is unduly high. With "standard" mortality rates (4% for resection of malignant nodules, 0.5% for removal of benign nodules), the differences in outcome, in terms of average life expectancy, between the needle biopsy and thoracotomy strategies are relatively miniscule over a wide range of values for the probability of malignancy.

In such situations, the desires of the patient may properly become paramount in management decisions. Some patients are "risk-averse" and prefer to avoid thoracotomy unless a diagnosis of malignancy has been established; needle aspiration as the initial procedure would usually be chosen in this circumstance. Conversely, patients who prefer to get the problem settled definitively and expeditiously would undoubtedly choose exploratory thoracotomy as the initial investigative procedure. As the two strategies are approximately equal in terms of average life expectancy, either choice is reasonable and appropriate.

I have recalculated the expected values for the needle biopsy strategy after modifying the decision tree to allow for the possibility of chest wall metastasis by needle track implantation, assuming an incidence of one such event in each thousand biopsies and a life expectancy after biopsy of only 1 year if implantation occurred. The average life expectancy of the needle biopsy strategy dropped, but only by a trivial amount. This is supportive of the clinical perception that tumor implantation after needle biopsy of the lung is a remote eventuality that need not carry major weight in the decision process.

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Surgical Resection for Complications of Pulmonary Tuberculosis

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From 1975 through 1984, 24 patients at the Medical University of South Carolina underwent surgical resection for complications of pulmonary tuberculosis. The complications fell into three major categories: persistent or drug-resistant disease, bronchiectasis, and hemoptysis. The major indications for surgical intervention included hemoptysis (14 patients), drug resistance (5), possible neoplasm (3), and bronchiectasis (2). Impaired pulmonary function was common. Surgical therapy generally necessitated lobectomy, sometimes resulted in substantial blood loss, and had a total major and minor complication rate of 46%. Despite these problems, the long-term prognosis after successful resection is good.

(Ann Thorac Surg 1989;48:165–7)

The history of thoracic surgery mirrors the history of tuberculosis, and for many surgeons, this disease and its complexities served as the training ground for the development of surgical skills. Today, the young thoracic surgeon can complete training with little exposure to this disease and little experience with surgical intervention. However, despite the success of chemotherapeutic agents in the management of pulmonary tuberculosis, complications of this disease will continue to present a challenge to the thoracic surgeon, especially in pockets of rural America and inner cities. A recent 10-year period was reviewed to assess the role and outcome of surgical resection for complications of pulmonary tuberculosis.

Material and Methods

The reports of the thoracic surgery service at the Medical University of South Carolina, Charleston, SC, were reviewed from 1975 through 1984. All patients undergoing pulmonary resection resulting from complications of tuberculosis were recorded and their charts and roentgenograms reviewed. Follow-up was obtained through review of clinic visits, written correspondence, and telephone calls. The patient population managed by the thoracic surgery service includes the Medical University Hospital, the Charleston Veterans Administration Hospital, and the Charleston County Memorial Hospital.

During the 10-year period, 24 patients underwent pulmonary resection for complications of tuberculosis. There were 22 men and 2 women (a ratio of 11:1). Mean age at the time of initial diagnosis of tuberculosis was 44.5 years (range, 20 to 60 years). Mean age at the time of surgical resection for complications was 54.5 years (range, 23 to 67 years).

Eighty-three percent of the patients were smokers; 14 (58%) of the 24 patients were considered heavy smokers, defined as smoking one or more packs per day or 50 pack-years or more. The most common associated disease was alcohol abuse (15 patients). Other associated conditions included hypertension (2 patients), diabetes mellitus (2 patients), and chronic renal insufficiency (1 patient).

Twenty-one patients had a past history of *Mycobacterium tuberculosis* infection. Three patients (12.5%) were infected with atypical organisms: *Mycobacterium avium intracellulare* (2) and *Mycobacterium gordonae* (1).

Drug therapy was considered appropriate in all patients except 3 with documented noncompliance. These 3 patients had *M tuberculosis* infection. Two of them were placed on a regimen of triple-drug therapy, but compliance was very questionable according to clinical records. The third patient, a migrant Hispanic, had been treated with unknown antituberculosis drugs for 6 months in a Mexican hospital. The remainder of the patients with *M tuberculosis* infection were treated for a minimum of 1.5 years except for 2 who received isoniazid (INH) for 1 year and 1 who received multidrug therapy for 6 months prior to the decision to intervene surgically. Five patients had single-drug treatment with INH. The 3 patients with atypical organisms had been treated with multiple drugs for more than 1.5 years secondary to documented drug resistance. Two patients with *M tuberculosis* infection had undergone previous drug treatment in sanatoriums and prior surgical resections more than 20 years before recurrence developed in the same lung field and led to complications.

There were 36 complications among the 24 patients, 12 patients having two complications. The complications fell into three major categories: (1) persistent or drug-resistant disease, 8 patients (33%); (2) bronchiectasis (verified in all instances by bronchograms), 12 patients (50%); and (3) hemoptysis, 16 patients (67%).

The most common complication requiring surgical intervention was hemoptysis (14 patients, 58%). It was considered massive, more than 500 mL per episode, in 6 patients. Bronchiectasis was thought to be a contributing factor in 7 of these patients. Chest roentgenograms

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showed cavitation in 11. Aspergilloma was eventually confirmed in 8 patients with hemoptysis.

Drug resistance constituted the reason for operative intervention in 5 patients (21%) including the 3 with atypical organisms. The possibility of neoplasm resulted in three resections (12.5%). Bronchiectasis, although common, was the primary indication for operation in only 2 patients (8%).

Preoperative cultures were positive for tuberculosis in 7 patients, including all patients showing drug resistance. Three patients had cultures positive for aspergillosis. Eighteen patients were on a regimen of preoperative antituberculosis chemotherapy at the time of operation, and 2 patients with positive cultures for aspergillosis were placed on a regimen of amphotericin B preoperatively. Three patients who were seen with hemoptysis and 1 patient in whom a neoplasm was suspected were not given preoperative antituberculosis therapy. The 2 patients with *M avium intracellulare* infection were maintained on INH, rifampin, and ethambutol hydrochloride; no second-line drugs were added. The 2 patients with resistant *M tuberculosis* infection and the patient with *M gordonae* were on four-drug and three-drug regimens, respectively, for 4 to 6 weeks prior to operation. Second-line drugs were included in these regimens. Except for 2 patients who received two preoperative doses of streptomycin A, the remaining patients were on a preoperative regimen that included INH combined with ethambutol or rifampin for a period ranging from two days to 6 months.

All but 3 patients had preoperative pulmonary function tests. The forced expiratory volume in 1 second was less than or equal to 50% of predicted in half of the tested patients. Only 3 patients had forced expiratory volume in 1 second greater than 75% of predicted.

Results

Surgical resection consisted of lobectomy in 13 patients, lobectomy with or without segmentectomy in 4, bilobectomy with or without segmentectomy in 2, completion pneumonectomy or pneumonectomy in 3, and resection of less than a lobe in 2. Thoracotomies were performed through standard posterolateral incisions. A double-lumen endobronchial tube was not used routinely, although it or an endobronchial blocker was employed occasionally when a patient had experienced active hemoptysis 24 hours before operation.

There were no intraoperative complications due to anesthesia. Estimated blood loss ranged from 300 to 4,000 mL (median loss, 1,150 mL). Although the operative reports often mentioned extensive adhesions and the necessity for tedious dissection, only two major intraoperative complications were documented. In 1 patient, the right pulmonary artery was lacerated and successfully repaired during a right upper lobectomy. In another patient, the pleural cavity and pulmonary fissures were totally obliterated, and attempted dissection resulted in parenchymal injury. Wedge resection of the lung apex was performed with a stapling device, as the patient could not tolerate a pneumonectomy.

Pathological specimens yielded seven cultures positive for tuberculosis, eight positive for aspergillosis, and 1 specimen positive for both. All patients with drug-resistant tuberculosis had positive cultures. One patient with localized *M avium intracellulare* infection was not placed on any postoperative drug therapy. The other 6 patients with pathological specimens yielding positive cultures remained on a three-drug or four-drug regimen for a minimum of 1 year. Eleven patients with postoperative cultures negative for tuberculosis were discharged on a regimen of INH alone or in combination with ethambutol or rifampin for a period of 6 weeks to 1 year. The 6 other patients with negative cultures were discharged without medications.

Table 1. Postoperative Complications

Complication	No. of Patients[a]	Operation
Major		
Bronchopleural fistula	1	Wedge resection
Empyema	2	Lobectomy
Pneumonia	1	Completion pneumonectomy
Total	4 (16.7)	
Minor		
Pleural effusion	1	Lobectomy
Superficial wound infection	2	Lobectomy
Atelectasis	3	Lobectomy
Mental confusion	1	Lobectomy
Total	7 (29.2)	

[a] Numbers in parentheses are percentages.

There were no postoperative deaths. Four major postoperative complications (17%) and seven minor complications (29%) occurred (Table 1). Major complications included bronchopleural fistula, empyema, and pneumonia. Half of them occurred in patients undergoing wedge resection or pneumonectomy. The rate of major complications for patients undergoing lobectomy was 10.5% (2/19).

Time from operation to discharge ranged from eight to 75 days (median time, 12.5 days). Three patients were lost to follow-up. Two patients had reactivation of disease in the opposite lung field. They were successfully treated medically, and follow-up sputum cultures were negative. The remaining 18 patients had no further pulmonary complaints from 2 to 12.5 years postoperatively (median follow-up, 5 years). Two patients have died of unrelated causes at 2 years and 11.5 years.

Comment

Indications for current surgical treatment of pulmonary tuberculosis were outlined by McLaughlin and Hankins [1] in 1974. Surgical criteria included (1) active localized disease unresponsive to chemotherapy, ie, persistent disease; (2) residual foci of disease prophylactically removed for various sociological and psychological factors; (3) the possibility of neoplasm; (4) various complications of tuberculosis, including empyema, bronchopleural fistula, and massive hemorrhage; and (5) management of complications after resection.

An absolute indication for surgical intervention is the presence of localized disease and sputum cultures that continue positive after adequate chemotherapy, a combined finding most often representing atypical mycobacterial disease. Many authors [2–5] have addressed the success of surgical management of atypical tuberculosis. Operative deaths are infrequent; there have been none in recent series. Total complication rates have been high (28.5% to 37.7%), but the incidence of major complications ranges from 0% to 14.2% [2–5]. In a 1983 report of resection for *Mycobacterium intracellulare* infection [5], only minor complications were encountered with no instances of bronchopleural fistula, wound infection, operative spread, or reexploration for bleeding. The rate of successful outcome is high (79%) in this category of persistent disease.

Persistent cavity as an isolated indication for surgical intervention has been mentioned in several reports [6, 7], but correlation with hemoptysis is lacking. It is well known that open-healed cavities can serve as the locus for mycetomas caused by predominantly *Aspergillus*. Such patients frequently are seen because of recurring and often severe bouts of hemoptysis [8, 9].

In our series, persistent hemoptysis was the primary indication for operation in more than half of the patients. The association with *Aspergillus* was particularly striking. There is suggestion that the diagnosis of an aspergilloma in a patient with tuberculosis is associated with a poor prognosis [8]. If a patient is seen with recurrent or progressive bleeding and has localized disease, we favor resection. This may have a favorable impact on short-term survival [8, 9].

Our series may well represent the typical patient the surgeon can expect to treat, whether in the inner city or rural America. The patient is often of poor socioeconomic status and in poor nutritional state. He or she is often a heavy smoker, and impaired pulmonary function is common. Indeed, Moran and associates [5] mentioned that only 30% to 40% of patients with *M intracellulare* infection were candidates for resection in part because of marginal pulmonary function. In our series, the forced expiratory volume in 1 second, used as a measure of major obstructive airway disease, was marginal in half of the tested patients. The incidence of alcoholism is high among patients with pulmonary tuberculosis.

We consider this population at increased risk for surgical complications. An early aggressive approach should be taken with patients seen with a persistent cavity and early hemoptysis. Attention to nutritional status may decrease the complication rate, and vigorous postoperative pulmonary care, including bronchoscopy, is of paramount importance. We favor the routine use of the double-lumen endotracheal tube, and consider it mandatory in cases of cavitary disease and hemoptysis. The major complication rate of 10.5% for lobectomy is not excessive considering this population of patients and in light of other reported series. The resection should be limited to lobectomy if possible.

In summary, in our series of surgical resection for complications of pulmonary tuberculosis, the indications for operation included hemoptysis, drug resistance, possible neoplasm, and bronchiectasis. The surgical therapy generally necessitated a lobectomy, at times resulted in substantial blood loss, and had a total complication rate of 46% (major complications, 16.7%). Despite the various problems, postoperative stay was not excessive and long-term prognosis after successful resection was good. It is anticipated that complications of pulmonary tuberculosis will continue to represent a challenge to the practicing thoracic surgeon.

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Effect of Prior Cardiac Surgery on Survival After Heart Transplantation

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We conducted a retrospective analysis of 182 adult orthotopic heart transplant patients who underwent operations at our institution between July 1982 and October 1987 to determine whether prior cardiac operation affects survival. Group I included the 72 patients (39.6%) who had undergone a previous cardiac operation or operations and group II, the 110 (60.4%) who had not. The mean age of the patients in group I was 52.1 ± 8.1 years and in group II, 46.1 ± 10.2 years ($p < 0.01$). The incidence of ischemic heart disease was 86.1% in group I and 29.1% in group II ($p < 0.01$). All patients received cyclosporine-based immunosuppression. More patients in group I than in group II required reoperation for bleeding after transplantation: 18 (25.0%) versus 9 (8.2%) ($p < 0.01$). The actuarial 1-year and 3-year survival rates were 77.6% and 66.5%, respectively, for group I and 77.1% and 66.3%, respectively, for group II. Because both groups had similar survival rates, we believe that prior cardiac operation in heart transplant recipients does not compromise long-term survival.

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As a result of improvements in heart transplantation, several groups of patients with end-stage cardiac disease are now considered appropriate candidates for this operation even though they are potentially at high risk [1–3]. One such group comprises patients with a history of prior cardiac operation who are believed to be at risk because they are generally older, and the cardiac transplant operation is theoretically more technically challenging because of previous median sternotomy [4–9]. This report details our extensive experience with this challenging group of heart transplant recipients and identifies their unique problems. Based on the findings of our retrospective review, we believe that these patients can benefit from transplantation as much as any other group of recipients.

Material and Methods

Between July 1982 and October 1987, we performed 209 heart transplantations with the recipients maintained on cyclosporine-based immunosuppression protocols. Of these recipients, 182 were adults who received an orthotopic heart transplant and who did not require mechanical circulatory support, other than an intraaortic balloon pump, either preoperatively or postoperatively. A retrospective analysis demonstrated that 72 (39.6%) had undergone prior cardiac operation (group I) and 110 (60.4%) had not (group II). Of the 72 patients in group I, 51 (70.8%) had undergone only one previous operation, whereas 19 patients (26.4%) had had two operations, and 2 patients (2.8%) had had three. The follow-up was similar for both groups (21.6 ± 16.4 months versus 22.3 ± 15.5 months, respectively).

Both groups comprised mostly men: 93.1% in group I and 82.7% in group II ($p < 0.05$). The mean age of patients in group I was 52.1 ± 8.1 years and in group II, 46.1 ± 10.2 years ($p < 0.01$).

Ischemic heart disease was the primary cause of cardiac dysfunction in group I (86.1%), whereas idiopathic cardiomyopathy was predominant in group II (66.4%) (Table 1). Of the patients in group I, 39 (54.2%) were on a regimen of antiplatelet medications before transplantation and 33 (45.8%) were not. The hemodynamic conditions of the patients were similar before transplantation, 52 (72.2%) in group I and 82 (74.5%) in group II were in stable condition. Eleven (15.3%) patients from group I and

Table 1. Causes of Cardiac Disease[a]

Cause	Group I (n = 72)	Group II (n = 110)
Ischemic[b]	62 (86.1)	32 (29.1)
Nonischemic[b]	10 (13.9)	78 (70.9)
Idiopathic	0	73
Valvular	7	0
Viral	0	3
Congenital	3	0
Familial	0	1
Chagas' disease	0	1

[a] Numbers in parentheses are percentages. [b] Significance: $p < 0.01$ between the two groups.

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Table 2. Maintenance Immunosuppression[a]

Immunosuppression Protocol	Group I	Group II
Double drug[b]	42 (58.3)	68 (61.8)
Triple drug[b]	19 (26.4)	25 (22.7)
Other[b]	11 (15.3)	17 (15.5)

[a] Numbers in parentheses are percentages. [b] Significance: p = not significant between the two groups.

19 (17.3%) from group II required pharmacological pressor support, and 9 from each group (12.5% and 8.2%, respectively) required intraaortic-balloon pump support. All patients in group I had received heterologous blood transfusions, whereas only 10.8% of group II patients had.

The pretransplantation incidence of renal impairment (serum creatinine level ≥ 2.0 mg/dL) was lower in group I (5.6%) than in group II (10.9%) (not significant [NS]). The pretransplantation incidence of liver impairment (total bilirubin ≥ 2.0 mg/dL) was also lower in group I (12.5%) than in group II (19.1%) (NS).

Maintenance immunosuppression protocols (Table 2) included cyclosporin A (14 mg/kg/day) and steroids. Elderly patients (age ≥ 55 years) and those with evidence of impaired renal function (creatinine clearance ≤ 55 mL/min or serum creatinine level ≥ 1.5 mg/dL) were maintained on triple-drug immunosuppression therapy consisting of cyclosporin A (10 mg/kg/day), steroids, and azathioprine (1 mg/kg/day). Rejection episodes were monitored by examining serial endomyocardial biopsy samples; the severity of rejection was assessed on a scale of 1 through 10 according to the scale of McAllister and associates [10] in which a grade of 5 or 6 denotes moderate rejection and grade 7 and higher, advanced rejection.

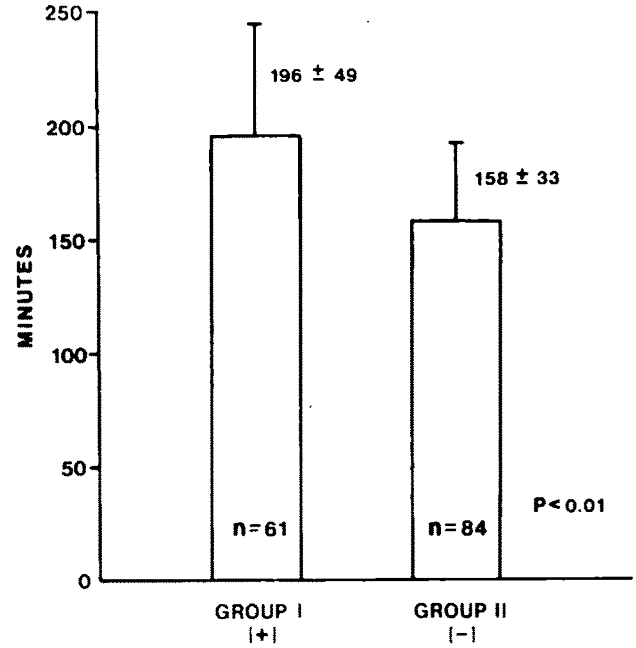


Fig 1. Length of cardiac transplant operation for groups I and II.

Statistical analyses were performed using the unpaired Student's t test, χ^2 analysis, and the Mantel-Haenszel test for life-table analysis.

Results

The duration of the entire operation, as well as cardiopulmonary bypass and aortic cross-clamp times, was significantly longer for group I patients ($p < 0.01$) (Figs 1, 2), 11 (15.3%) of whom underwent femorofemoral cannulation. The incidence of reoperation for bleeding was significantly higher in group I than in group II (18 [25.0%]

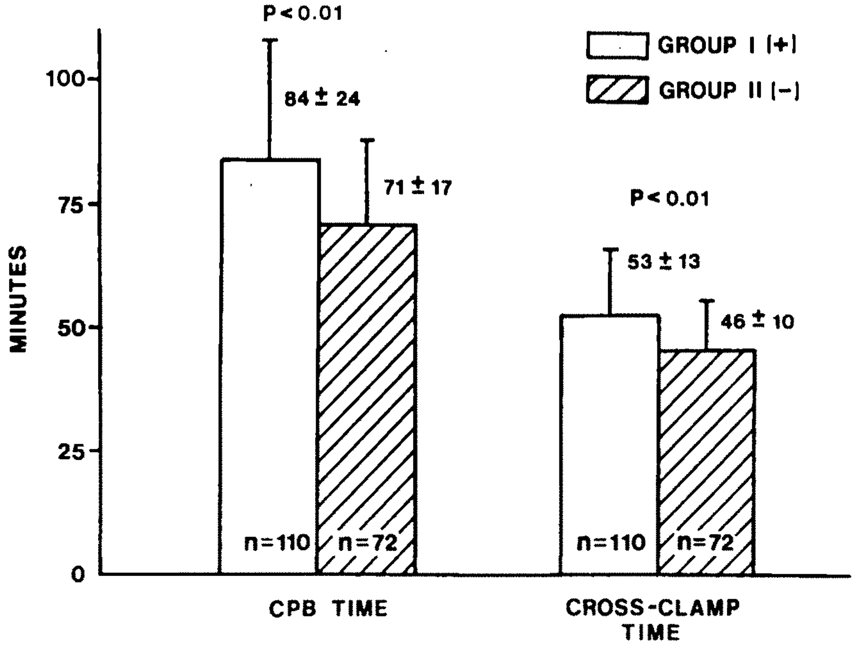


Fig 2. Length of cardiopulmonary bypass (CPB) and aortic cross-clamping during the cardiac transplant operation for groups I and II.

Table 3. Advanced Rejection Episodes[a,b]

No. of Rejection Episodes	Group I	Group II
0	37 (51.4)	61 (55.5)
1	33 (45.8)	33 (30.0)
≥2[c]	2 (2.8)	16 (14.5)

[a] This means an endomyocardial biopsy score of 7 or greater. [b] Numbers in parentheses are percentages. [c] Significance: $p < 0.05$ between the two groups.

Table 4. Causes of Death[a]

Cause	Group I	Group II
Rejection	2 (9.5)	7 (20.0)
Graft atherosclerosis	4 (19.0)	9 (25.7)
Infection[b]	11 (52.4)	9 (25.7)
Multisystem failure	4 (19.0)	4 (11.4)
Other	0 (0)	6 (17.1)
Total	21 (29.2)	35 (31.8)

[a] Numbers in parentheses are percentages. [b] Significance: $p < 0.05$ between the two groups.

versus 9 [8.2%]; $p < 0.01$), but there was no significant difference in the incidence of mediastinitis (5.6% versus 4.5%, respectively), ie, positive deep wound cultures associated with wound drainage and sternal instability necessitating operative repair.

The posttransplantation incidence of renal dysfunction increased transiently in both groups (51.4% versus 57.3%, group I versus group II), but peak creatinine levels within 30 days after transplantation were similar (2.4 ± 1.2 mg/dL versus 2.5 ± 1.2 mg/dL, respectively; NS). After transplantation, the incidence of liver impairment increased more in group I than in group II (80% versus 75.7%; NS). Peak total bilirubin levels after transplantation were similar in both groups (4.9 ± 4.2 mg/dL versus 4.7 ± 5.1 mg/dL, group I versus group II; NS).

Maintenance immunotherapy was similar between the two groups (see Table 2), as were the median serum cyclosporine trough levels at 1 and 2 weeks after transplantation. At 1 week, the levels were 262 ± 165 ng/mL for group I and 266 ± 148 ng/mL for group II (NS), and at 2 weeks they were 317 ± 180 ng/mL and 356 ± 166 ng/mL (NS), respectively. The incidence of advanced allograft rejection (endomyocardial biopsy score ≥ 7) was similar in both groups (0.5 ± 0.6 versus 0.7 ± 0.9, group I versus group II); however, 14.5% of group II patients had two or more advanced rejection episodes compared with 2.8% of group I patients ($p < 0.05$) (Table 3).

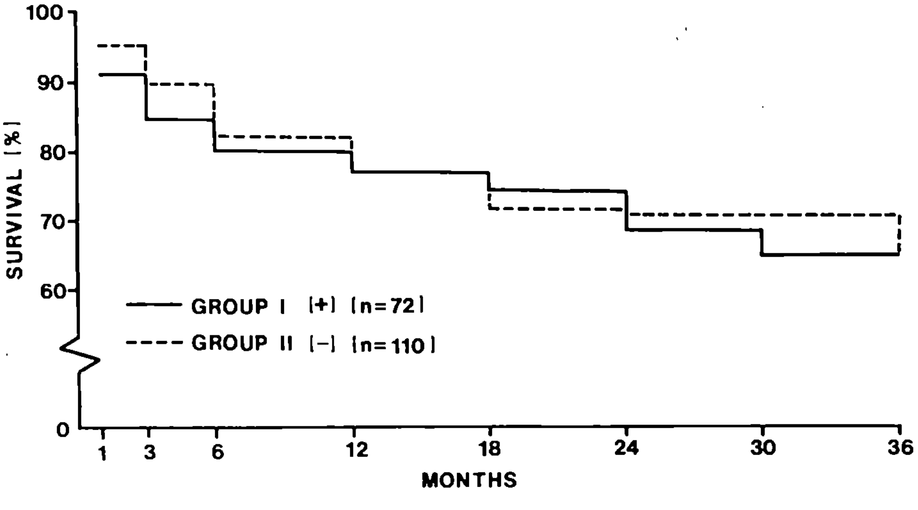
There was no significant difference in early mortality (30 days) between the groups (8.3% versus 4.6%, group I versus group II). Moreover, early mortality was similar for group I patients who had had one prior sternotomy compared with those who had had two or more (9.1% versus 7.8%, respectively). The percentage of deaths resulting from rejection was slightly lower in group I, but there was no significant difference between the groups in regard to deaths resulting from graft atherosclerosis (Table 4). The incidence of deaths caused by infection was higher in group I than in group II ($p < 0.05$).

The actuarial 1-year, 2-year, and 3-year survival rates were 77.6%, 69.5%, and 66.5%, respectively, for group I and 77.1%, 71.5%, and 66.3%, respectively, for group II (Fig 3). In addition, there was no significant difference in the actuarial 1-year and 2-year survival rates between group I patients with one prior cardiac procedure (76.2% and 68.1%, respectively) versus those with multiple prior cardiac operations (80.1% and 71.4%, respectively) (Fig 4).

Comment

Cardiac transplantation remains an accepted therapy for end-stage cardiac disease resulting from both ischemic and nonischemic causes. In 1987, 1,436 heart transplantations were performed in the United States at 109 centers [11]. Because the present donor supply is limited and, thus, is a primary determinant of the future of heart transplantation, analyzing the risk factors associated with morbidity and mortality is helpful in identifying patients most likely to benefit from the procedure [12]. One such

Fig 3. Actuarial survival rates for groups I and II.



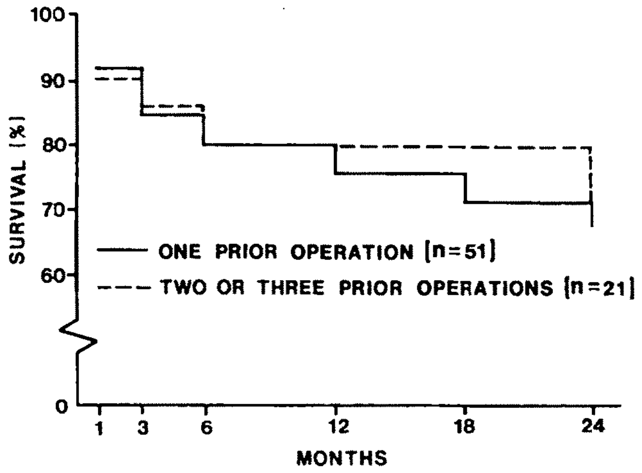


Fig 4. Comparison of actuarial survival rates of group I patients based on the number of previous cardiac operations.

risk factor is a history of prior cardiac operation. Because group I patients were older and the primary cause of their end-stage cardiac disease was ischemic cardiomyopathy that had required previous surgical treatment, and, therefore, repeat median sternotomy at transplantation, we thought that these patients might not fare as well as others [1–9].

Despite similar postoperative survival rates for groups I and II, perioperative morbidity, notably reoperation for bleeding, was more prevalent in group I. In most patients, a specific bleeding site resulting from a technical fault could not be identified. The preoperative ingestion of antiplatelet medications appears to be a significant factor in this issue. Of the 18 patients in group I requiring exploration for bleeding, 15 (83.3%) had been on a regimen of antiplatelet medication. However, of the 64 patients in group I who did not require reexploration, only 28 (43.8%) had been taking aspirin preoperatively ($p < 0.01$).

Although the overall survival rates were the same in these two subsets of group I patients, the data concur with those in other reports demonstrating the adverse effect of antiplatelet medications on postoperative bleeding in patients undergoing cardiac operation [13]. Because some reports [14, 15] have shown that the use of antiplatelet therapy in patients who have ischemic heart disease or who have undergone prior coronary artery bypass grafting can be beneficial, discontinuing the medications once a patient is placed on the active transplant list might not be advisable.

Despite the use of similar early maintenance immunosuppression for groups I and II, group I patients experienced fewer advanced rejection episodes. A clue to this disparity may be found in the difference between the two groups in terms of previous heterologous blood transfusions. Kerman and associates [16] demonstrated the benefits of such transfusions in certain cardiac transplant recipients. A closer look at human lymphocyte antigens in cardiac transplant recipients may be warranted.

In both groups, deaths most often resulted from either graft atherosclerosis or overwhelming infections. Despite the high incidence of ischemic cardiomyopathy as the preexisting cardiac disease in group I patients, the number of deaths resulting from graft atherosclerosis in group I was not significantly different from that in group II. These data imply that graft atherosclerosis may have an immunological basis in addition to, or instead of, other local or environmental factors [17].

Finally, more patients in group I died of infection. We attribute this fact to the larger percentage of older patients in group I, patients who are less likely to tolerate serious infections, especially when they are immunosuppressed. This phenomenon may depend on differences in cyclosporine pharmacokinetics between older and younger patients [18].

This study supports the common practice of considering patients who have undergone prior cardiac operation candidates for transplantation. Although they are generally older and have a history of atherosclerosis, their outcome was comparable with that of other cardiac transplant recipients in terms of both short-term and long-term survival.

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DISCUSSION

DR W. STEVES RING (Dallas, TX): I thank the authors for allowing me to review their manuscript in advance.

Dr Lammermeier and his colleagues at the Texas Heart Institute are to be congratulated on a superb presentation and a very careful analysis of one of the largest heart transplant experiences using cyclosporine-based immunosuppression. They have concluded that prior heart operation does not have a major impact on either early or long-term mortality following orthotopic heart transplantation.

Their findings stimulated me to review my personal series of 110 orthotopic cardiac transplantations performed over a 4-year period, 1984 to 1988, first at the University of Minnesota and more recently at the University of Texas Southwestern Medical Center in Dallas. In my series of 110 patients, there were 3 hospital deaths, an operative mortality of less than 3%, and 2 late deaths, which were due to chronic rejection. Both late deaths occurred in patients who were abusing alcohol in spite of repeated warnings. Thirty-four percent of the patients had a history of prior heart operation. There were no hospital deaths in this group, and the 1-year survival rate was 100%. There was 1 late death at 18 months, which was due to chronic rejection. Among the 73 patients without a previous heart operation, there were 3 hospital deaths and 1 late death at 6 months, a 94% 1-year survival rate.

However, in contrast to the experience of the Houston group, fewer than 5% of the recipients required reoperation for bleeding, and as opposed to the 5% to 6% incidence of mediastinitis, none of my patients had mediastinitis. My colleagues and I take extra time to carefully dissect the recipient's old heart at reoperation to minimize the need for perioperative blood products and reduce the risks of reexploration and mediastinitis, even if it means prolonging donor ischemic time by 20 or 30 minutes.

Dr Lammermeier and his colleagues observed no difference in the frequency of acute rejection between their two groups, with about half the patients in each group being treated for rejection. However, the patients who have had previous operation seem to be less likely to experience multiple rejection episodes. We have observed only one acute rejection episode among the 37 patients with prior operation, a 3% incidence of acute rejection, but 8 of the 73 patients without a previous operation, or 11%, required treatment for a single rejection episode.

It is unclear to me whether this difference in the incidence of acute rejection is due to the older age with reduced immune responsiveness of the recipients who have had a previous operation, most of whom have ischemic heart disease, or whether it might relate to the higher incidence of prior blood transfusions in this group, as blood transfusions have been shown to reduce the incidence of rejection in renal transplant recipients.

I have three questions for Dr Lammermeier. First, with such a high incidence of reexploration for bleeding and of mediastinitis, how have you altered your technique to reduce this morbidity? Second, do you think that prior blood transfusion confers additional immunosuppressive benefit in cardiac transplant recipients as it does in renal transplant recipients? Third, are the differences in infection-related versus rejection-related deaths between the two groups attributable to the reoperative status or purely to the difference in age between the two groups?

Again, I congratulate the authors on an important contribution to the heart transplant literature.

DR LAMMEMEIER: I thank Dr Ring for his kind comments.

We did have a high incidence of reoperation for hemorrhage in the patients who had undergone prior cardiac operation. The data base for this report, however, begins in 1982. As we have gained experience in dealing with transplant recipients and advances have been made in identifying and correcting coagulation deficiencies, we have experienced fewer bleeding difficulties. In addition, we have recently recommended the discontinuation of antiplatelet medications in many candidates on the active transplant list. There was a higher incidence of death from infection in group I patients, and this may have occurred because those patients were older. Elderly patients are more prone to infection, especially when they are immunosuppressed. Moreover, studies of bone marrow transplant recipients propose an alteration in the cyclosporine pharmacokinetics of the elderly patient group, and we wonder whether this may play a role in elderly cardiac transplant recipients as well.

I reiterate that we support the continued practice of analyzing patient subsets in regard to continued inherent risk factors before transplantation. Through such studies, the conditions that define both higher or lower risk may be discovered, and this may influence the selection of proper recipient candidates for an ever-increasing, but limited, donor pool.

Cardiac Valve Replacement in the Elderly: Clinical Performance of Biological Prostheses

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Robert T. Miyagishima, MD, and Alfred N. Gerein, MD

Vancouver General Hospital and St. Paul's Hospital, The University of British Columbia, Vancouver, British Columbia, Canada

From 1975 to 1987, 1,127 elderly patients underwent 1,223 valve replacements with the Carpentier-Edwards standard or supraannular porcine bioprostheses in 1,147 operations. Of the total patient population seen during these years, 33.5% receiving a standard porcine bioprosthesis and 48.6% receiving a supraannular bioprosthesis were 65 years of age or older. Of this elderly patient population, 465 patients were between 65 and 69 years old; 618 patients, 70 and 79 years old; and 52 patients, 80 years old and older. Aortic valve replacement was performed in 635 patients, mitral valve replacement in 417 patients, tricuspid valve replacement in 2 patients, and multiple-valve replacement in 80 patients. The cumulative follow-up was 3,957 patient-years. Early mortality was 9.5%: 7.3% for the 65- to 69-year-old group, 10.7% for the 70- to 79-year-old group, and 15.4% for the group 80 years old and older. Late mortality was 5.5% per patient-year: 4.2% per patient-year for the 65- to 69-year-old group, 6.3% per patient-year for the 70- to 79-year-old group, and 14.1% per patient-year for the group 80 years old and older. Valve-related causes contributed to 7 early deaths and 33 late deaths. The overall patient survival, including operative deaths, was 70.7% ± 1.6% at 5 years and 47.8% ± 3.7% at 10 and 12 years. The freedom from all valve-related complications was 52.1% ± 6.1% at 10 and 12 years. The overall rate of valve-related complications was 5.0% per patient-year (fatal complications, 1.13% per patient-year). The overall rate of thromboembolism was 2.3% per patient-year and the freedom from thromboembolism, 69.6% ± 5.2% at 10 and 12 years. The freedom from structural valve deterioration was 80.8% ± 8.1% at 10 and 12 years: 71.7% ± 11.0% at 10 and 12 years for the 65- to 69-year-old group, 97.9% ± 1.2% at 10 years for the 70- to 79-year-old group, and 100% at 12 years for the group 80 years old and older. At 10 and 12 years, the freedom from valve-related death was 83.7% ± 4.3% and the freedom from reoperation, 73.3% ± 8.6%. The freedom from valve-related death, residual morbidity from thromboembolism and anticoagulant-related hemorrhage, and reoperation was 61.7% ± 7.0% at 10 and 12 years. The clinical performance of porcine bioprostheses in the elderly patient population has been excellent. The early mortality increases in patients 70 years old or older. Structural valve deterioration is essentially nonexistent at 10 and 12 years in patients 70 years of age or older.

(Ann Thorac Surg 1989;48:173–85)

Documentation of valvular cardiac surgery in the elderly population has consisted chiefly of evaluation of early and late mortality in justification of the operation [1–28].The quality of life of this patient population has also been given considerable attention [3, 4, 6–8, 12, 13, 17–19]. Detailed evaluation of valve-related complications with either biological or mechanical prostheses has not been performed. The experience of The University of British Columbia with cardiac valve replacement was originally documented in 1980 [14] and 1981 [15]. The role of porcine bioprostheses is presented here in an evaluation of 1,127 consecutive patients aged 65 years and older.

Material and Methods

The teaching hospitals of The University of British Columbia, Vancouver General Hospital and St. Paul's Hospital, have used porcine bioprostheses since 1975. From 1975 to 1987, the Carpentier-Edwards standard porcine bioprosthesis was implanted in 1,183 patients and the Carpentier-Edwards supraannular porcine bioprosthesis, in 1,536 patients. Of the total patient population, 41.4% were 65 years of age and older, 33.5% of the patients receiving a standard bioprosthesis between 1975 and 1982 and 48.6% of the population given a supraannular bioprosthesis from 1982 to 1987.

The elderly patient population is detailed in Tables 1 through 4. There were 1,127 patients who received 1,223

Table 1. Patient Population by Age

Age (yr)	Total Patients	Total Operations	Total Valves
65–69	465	469	501
70–79	618	626	669
≥80	52	52	53
Total	1,127[a]	1,147	1,223

[a] Eight patients are in both the 65- to 69-year-old group and the 70- to 79-year-old group.

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Table 2. Patient Population by Valve Replaced

Type of Valve Replacement	Total Patients	Total Operations	Total Valves
Aortic	635	636	636
Mitral	417	429	429
Tricuspid	2	2	2
Multiple	80	80	156[a]
Total	1,127[b]	1,147	1,223

[a] This represents 69 aortic valves, 79 mitral valves, and 8 triscupid valves. [b] Five patients are in both the aortic and mitral valve replacement groups, 1 patient is in both the aortic valve and multiple-valve replacement groups, and 1 is in both the mitral and multiple-valve replacement groups.

valves in 1,147 operations. Four hundred sixty-five patients were between 65 and 69 years old, 618 were between 70 and 79 years old, and 52 were 80 years old and older (see Table 1). Aortic valve replacement (AVR) was performed in 635 patients, mitral valve replacement (MVR) in 417 patients, tricuspid valve replacement in 2 patients, and multiple-valve replacement in 80 patients (see Table 2). The distribution of patients in the Carpentier-Edwards porcine standard and supraannular bioprostheses subsets is shown in Tables 3 and 4.

The average follow-up for the three age groups was 3.9 years for patients 65 to 69 years old, 3.2 years for patients 70 to 79 years old, and 2.5 years for the group 80 years old or more. The cumulative follow-up was 3,956.7 patient-years: 1,845.7 patient-years for the 65- to 69-year-old group, 1,983.2 patient-years for the 70- to 79-year-old group, and 127.8 patient-years for the group 80 years old or older (Table 5). Of the cumulative follow-up, AVR accounted for 2,329.1 patient-years; MVR, 1,397.2 patient-years; and multiple-valve replacement, 222.8 patient-years (Table 6).

Results

Early mortality was 9.5% (109 patients): 7.3% for the 65- to 69-year-old group, 10.7% for the 70- to 79-year-old group, and 15.4% for the group 80 years old or more (Table 7). Forty patients undergoing AVR died, 58 having MVR died, and 11 undergoing multiple-valve replacement died (Table 8). The causes of early death are detailed in Table 9. The valve-related causes included thromboembolism (3 patients), prosthetic valve endocarditis (1 patient), paraprosthetic leak (2), and hemorrhage as a result of antithromboembolic therapy (1).

Early mortality was influenced by concomitant procedures and previous cardiac operations. Early mortality was 12.8% among patients with concomitant procedures and 6.8% among those without additional procedures (Table 10), and 13.2% among patients with previous cardiac operations and 9.2% among those without such operations (Table 11). The causes of early death by age group are documented in Table 12.

Late mortality expressed as a linearized occurrence rate was 5.5% per patient-year overall; it was 4.2% per patient-year for the 65- to 69-year-old group, 6.3% per patient-year for the 70- to 79-year-old group, and 14.1% per patient-year for patients 80 years old or more (Table 13). Late mortality for AVR was 5.2% per patient-year; for MVR, 6.2% per patient-year; and for multiple-valve replacement, 5.4% per patient-year (Table 14). The causes of late death are shown in Table 15. The valve-related causes included thromboembolism (19 patients), prosthetic valve endocarditis (5), paraprosthetic leak (1 patient), hemorrhage due to antithromboembolic therapy (4), clinical valve dysfunction (1), and structural valve deterioration (3).

Overall patient survival, including operative deaths, was 70.7% ± 1.6% at 5 years and 47.8% ± 3.7% at 10 and 12 years (Fig 1). For the group 65 to 69 years old, survival was 77.5% ± 2.1% at 5 years and 60.9% ± 4.4% at 10 and 12 years; for the group 70 to 79 years old, survival was 67.6% ± 2.3% at 5 years; and for the group 80 years old or more, survival was 37.7% ± 6.2% at 3 years.

The freedom from all valve-related complications, mor-

Table 3. Patient Population for Carpentier-Edwards Standard Bioprosthesis

Age Group (yr)	Total Patients	Total Operations	Total Valves
65–69	192	195	205
70–79	189	190	196
≥80	15	15	15
Total	396[a]	400	416

[a] Three patients are in the 65- to 69-year-old group twice, and 1 patient is in the 70- to 79-year-old group twice.

Table 4. Patient Population for Carpentier-Edwards Supraannular Bioprosthesis

Age Group (yr)	Total Patients	Total Operations	Total Valves
65–69	274	275	296
70–79	435	438	473
≥80	37	37	38
Total	746[a]	750	807

[a] One patient is in the 65- to 69-year-old group twice, and 3 patients are in the 70- to 79-year-old group twice.

Table 5. Cumulative Follow-up by Age

Age (yr)	Total Operations	Total Patient-Years
65–69	469	1,845.7
70–79	626	1,983.2
≥80	52	127.8
Total	1,147	3,956.7

Table 6. Cumulative Follow-up by Valve Replaced

Type of Valve Replacement	Total Operations	Total Patient-Years
Aortic	636	2,239.1
Mitral	429	1,397.2
Tricuspid	2	7.6
Multiple	80	222.8
Total	1,147	3,956.7

Table 8. Early Deaths By Valve Replaced[a]

Type of Valve Replacement	Total Operations	Total Deaths	%
Aortic	636	40	6.3
Mitral	429	58	13.5
Tricuspid	2	0	0
Multiple	80	11	13.8
Total	1,147	109	9.5

[a] Early mortality is 30-day mortality.

bidity and mortality, was 52.1% ± 6.1% at 10 and 12 years (Fig 2). At 10 years, the freedom from all valve-related complications was 50.9% ± 8.3% for the 65- to 69-year-old group, 53.8% ± 8.5% for 70- to 79-year-old group, and 56.4% ± 23.6% for the group 80 years old and older. The hazard intervals by year indicating yearly rates and mortality rates are demonstrated in Figure 2.

The linearized occurrence rate for valve-related complications was 5.0% per patient-year (163 events) and the mortality rate, 1.13% per patient-year (40 events). The overall rate for valve-related complications was 4.0% per patient-year for the 65- to 69-year-old group (0.7% per patient-year, fatal), 4.4% per patient-year for the 70- to 79-year-old group (1.2% per patient-year, fatal), and 3.9% per patient-year for the group 80 years old or older (3.2% per patient-year, fatal).

The linearized occurrence rate and number of events for all valve-related complications are shown in Table 16 by age group and in Table 17 by valve replaced. The overall rates were as follows: thromboembolism, 2.3% per patient-year (92 events); antithromboembolic therapy–related hemorrhage, 0.6% per patient-year (23 events); prosthetic valve endocarditis, 0.3% per patient-year (11 events); paraprosthetic leak, 0.3% per patient-year (12 events); structural valve deterioration, 0.4% per patient-year (15 events); and clinical valve dysfunction, 0.3% per patient-year (ten events). The mortality rate for thromboembolism was 0.6% per patient-year (22 deaths); antithromboembolic therapy–related hemorrhage, 0.1% per patient-year (5 deaths); prosthetic valve endocartidis, 0.2% per patient-year (6 deaths); paraprosthetic leak, 0.08% per patient-year (3 deaths); structural valve deterioration, 0.08% per patient-year (3 deaths); and clinical valve dysfunction, 0.03% per patient-year (1 death).

Reoperation for valve-related complications was performed in 33 patients (0.8% per patient-year) (see Table 16). The linearized occurrence rate for AVR was 0.3% per patient-year (eight events); for MVR, 1.6% per patient-year (22 events); and for multiple-valve replacement, 1.4% per patient-year (three events) (see Table 17). The mortality rate for reoperation was 0.2% per patient-year (7 deaths). Of the 7 patients who died, reoperation was necessary for structural valve deterioration (3), prosthetic valve endocarditis (2), paraprosthetic leak (1), and clinical valve dysfunction (1).

Table 7. Early Deaths by Age[a]

Age (yr)	Total Operations	Total Deaths	%
65–69	469	34	7.3
70–79	626	67	10.7
≥80	52	8	15.4
Total	1,147	109	9.5

[a] Early mortality is 30-day mortality.

The morbidity and mortality associated with thromboembolism by age group are detailed in Table 18. The overall linearized occurrence rate for major events was 1.6% per patient-year (64 events). The overall linearized rate for minor events was 0.7% per patient-year (28 events). The mortality rate for the group 65 to 69 years old was 0.3% per patient-year (6 deaths); for the group 70 to 79 years old, 0.7% per patient-year (14 deaths); and for the group 80 years old or more, 1.6% per patient-year (2 deaths). The morbidity and mortality associated with thromboembolism are also detailed by valve replaced (Table 19).

The freedom from individual valve-related complications is shown in Figures 3 through 10. The linearized occurrence rate of each complication, depicting total and fatal events, by yearly hazard intervals is also illustrated

Table 9. Causes of Early Death

Cause	No. of Patients
Myocardial infarction/arrhythmia	28
Low output syndrome/congestive heart failure	35
Thromboembolism	3
Prosthetic valve endocarditis	1
Paraprosthetic leak	2
Antithromboembolic therapy–related hemorrhage	1
Hemorrhage	16
Aortic dissection	1
Other	22
Total	109[a]

[a] This represents 40 deaths among patients having aortic valve replacement, 58 deaths among patients having mitral valve replacement, and 11 deaths among patients having multiple-valve replacement.

Table 10. Early Deaths With and Without Concomitant Procedure

Type of Valve Replacement	With			Without		
	Operations	%	Deaths	Operations	%	Deaths
Aortic	30	9.7	29	334	3.3	11
Mitral	197	18.3	36	228	9.7	22
Tricuspid	1	0	0	1	0	0
Multiple	27	7.4	2	53	17.0	9
Total	525	12.8	67	616	6.8	42

Table 11. Early Deaths With and Without Previous Cardiac Procedure

Type of Valve Replacement	With			Without		
	Operations	%	Deaths	Operations	%	Deaths
Aortic	38	5.3	2	596	6.4	38
Mitral	64	18.8	12	361	12.7	46
Tricuspid	1	0	0	1	0	0
Multiple	11	9.1	1	69	14.5	10
Total	114	13.2	15	1,027	9.2	94

for each complication. The freedom from thromboembolism was 69.6% ± 5.2% overall at 10 and 12 years (see Fig 3). The freedom for the 65- to 69-year-old group was 78.2% ± 5.9% at 10 and 12 years; for the 70 to 79-year-old group, 90.8% ± 1.5% at 5 years; and for the group 80 years and older, 88.8% ± 7.6% at 5 years. The freedom from thromboembolism by valve replaced is shown in Figure 4. The freedom for AVR was 65.5% ± 6.5% at 10 and 12 years; for MVR, 79.3% ± 5.5% at 10 years; and for multiple-valve replacement, 97.0% ± 2.1% at 10 years. Thromboembolism and related deaths occurred throughout the observation period with a trend toward increased occurrence in the latter years of the period.

The freedom from hemorrhage related to antithromboembolic therapy was 97.6% ± 0.6% at 5 years and 95.3% ± 1.3% at 10 and 12 years (see Fig 5). There was no appreciable difference between the three age groups. This complication occurred throughout the observation period. The freedom from prosthetic valve endocarditis was 99.1% ± 0.3% at 5 years and 97.7% ±0.9% at 10 and 12 years (see Fig 6). Again, there was no difference between the age groups. This complication occurred early and midterm in the observation period. The freedom from paraprosthetic leak was 98.8% ± 0.4% at 5 years and 98.2% ± 0.7% at 10 and 12 years (see Fig 7). Paraprosthetic leak occurred only in the 65- to 69-year-old and 70- to 79-year-old groups.

The freedom from clinical valve dysfunction was 98.8% ± 0.4% at 5 years and 95.9% ± 2.6% at 10 and 12 years (see Fig 8). This complication occurred only in the 65- to 69-year-old and 70- to 79-year-old groups. The freedom from structural valve deterioration was 99.1% ± 0.4% at 5 years and 80.8% ± 8.1% at 10 and 12 years (see Fig 9). The freedom for the 65- to 69-year-old group was 71.7% ± 11.0% at 10 and 12 years; for the 70- to 79-year-old group, 97.9% ± 1.2% at 10 years; and for the group 80 years old and older, 100% at 12 years. The freedom from structural

Table 12. Causes of Early Death by Age

Cause	Age (yr)		
	60–69	70–79	≥80
Myocardial infarction/arrhythmia	6	17	5
Low output syndrome/ congestive heart failure	14	18	3
Thromboembolism	1	2	0
Prosthetic valve endocarditis	1	0	0
Paraprosthetic leak	0	2	0
Antithromboembolic therapy–related hemorrhage	1	0	0
Hemorrhage	6	10	0
Aortic dissection	0	1	0
Other	5	17	0
Total	34	67	8

Table 13. Late Deaths by Age

Age (yr)	Total Patient-Years	Total Deaths	%/Patient-Year
65–69	1,845.7	77	4.2
70–79	1,983.2	124	6.3
≥80	127.8	18	14.1
Total	3,956.7	219	5.5

Table 14. Late Deaths by Valve Replaced

Type of Valve Replacement	Total Patient-Years	Total Deaths	%/Patient-Year
Aortic	2,329.1	120	5.2
Mitral	1,397.2	86	6.2
Tricuspid	7.6	1	13.2
Multiple	222.8	12	5.4
Total	3,956.7	219	5.5

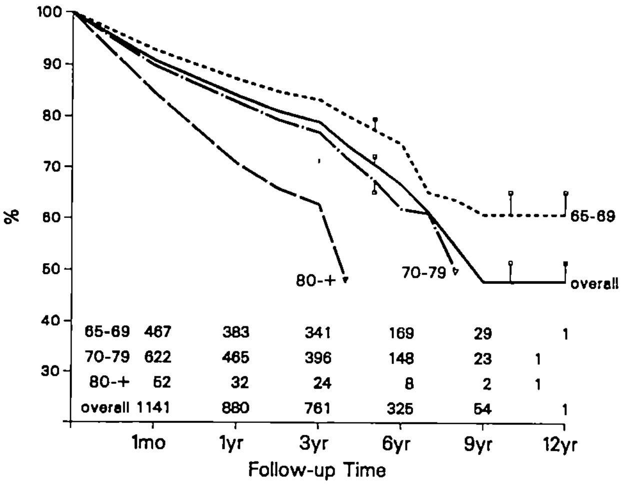

Fig 1. Patient survival.

valve deterioration for AVR was 99.4% ± 0.6% at 10 and 12 years; for MVR, 98.3% ± 1.0% at 5 years; and for multiple-valve replacement, 95.2% ± 4.6% at 5 years (see Fig 10). Structural valve deterioration commenced at 4 years and increased yearly, with a large increase during the tenth year of observation.

The multiple decrement analysis of valve-related complications is shown in Figures 11 through 16. The freedom from reoperation was 97.8% ± 0.6% at 5 years and 73.3% ± 8.6% at 10 and 12 years (see Fig 11). The freedom from reoperation at 10 and 12 years was 63.3% ± 11.2% for the 65- to 69-year-old group, 94.5% ± 1.8% for the 70- to 79-year-old group, and 100% for the group 80 years old and older. Reoperation occurred throughout the observation period, but the late increase parallels structural valve deterioration. The freedom from valve-related death was 96.3% ± 0.7% at 5 years and 83.7% ± 4.3% at 10 and 12 years (see Figs 12, 13). The freedom from death was 90.2% ± 4.5% at 10 and 12 years for the 65- to 69-year-old group, 77.5% ± 8.2% at 10 years for the 70- to 79-year-old group, and 59.5% ± 24.7% at 10 years for the group 80 years old and older (see Fig 12). Death from valve-related causes occurred throughout the observation period but increased late with reoperation and the higher rate of thromboem-

Table 15. Causes of Late Death

Cause	No. of Patients
Myocardial infarction/arrhythmia	40
Congestive heart failure	40
Thromboembolism	19
Prosthetic valve endocarditis	5
Paraprosthetic leak	1
Structural valve deterioration	3
Antithromboembolic therapy–related hemorrhage	4
Clinical valve dysfunction	1
Gastrointestinal hemorrhage	3
Hemorrhage	1
Sepsis	3
Sudden unexpected death (arrhythmia)	23
Noncardiac-related cause	20
Other	56
Total	219[a]

[a] This represents 120 deaths among patients having aortic valve replacement, 86 deaths among patients having mitral valve replacement, 1 death among patients having tricuspid valve replacement, and 12 deaths among patients having multiple-valve replacement.

Table 16. Linearized Occurrence Rates of Valve-Related Complications by Age[a]

	Age (yr)			
Morbidity, Mortality	65–69	70–79	≥80	Overall
Thromboembolism				
Overall	34 (1.8)	55 (2.8)	3 (2.4)	92 (2.3)
Fatal	6 (0.3)	14 (0.7)	2 (1.6)	22 (0.6)
Antithromboembolic therapy–related hemorrhage				
Overall	12 (0.7)	10 (0.5)	1 (0.8)	23 (0.6)
Fatal	3 (0.2)	1 (0.05)	1 (0.8)	5 (0.1)
Clinical valve dysfunction				
Overall	5 (0.3)	5 (0.3)	0	10 (0.3)
Fatal	0	1 (0.05)	0	1 (0.03)
Prosthetic valve endocarditis				
Overall	4 (0.2)	6 (0.3)	1 (0.8)	11 (0.3)
Fatal	1 (0.05)	4 (0.2)	1 (0.8)	6 (0.2)
Paraprosthetic leak				
Overall	6 (0.3)	6 (0.3)	0	12 (0.3)
Fatal	1 (0.05)	2 (0.1)	0	3 (0.08)
Structural valve deterioration				
Overall	12 (0.7)	3 (0.2)	0	15 (0.4)
Fatal	2 (0.1)	1 (0.05)	0	3 (0.08)
Reoperation				
Overall	20 (1.1)	13 (0.7)	0	33 (0.8)
Fatal	3 (0.2)	4 (0.2)	0	7 (0.2)

[a] Data in parentheses are percent per patient-year or episodes per 100 patient-years.

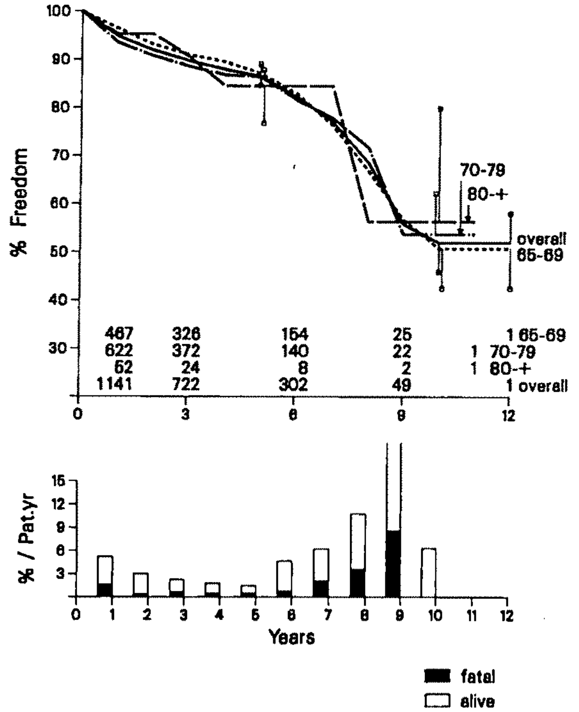

Fig 2. Freedom from all valve-related complications.

bolism. The freedom from valve-related death was 84.2% ± 5.2% for AVR at 10 and 12 years, 80.6% ± 9.4% for MVR at 10 years, and 96.5% ± 2.5% for multiple-valve replacement at 10 years (see Fig 13).

The freedom from valve-related death and reoperation was 94.6% ± 0.9% at 5 years and 64.3% ± 8.0% at 10 and 12 years (see Fig 14). The freedom for the 65- to 69-year-old group was 61.2% ± 10.8% at 10 and 12 years; for the 70- to 79-year-old group, 74.4% ± 8.0% at 10 years; and for the group 80 years old and older, 59.5% ± 24.7% at 8 and 10 years. The hazard rates parallel the rates of structural valve deterioration and deaths related to reoperation.

The freedom from valve-related death and residual morbidity (treatment failure) was 92.8% ± 1.0% at 5 years and 75.4% ± 4.5% at 10 and 12 years (see Fig 15). The freedom for the 65- to 69-year-old group was 81.8% ± 5.4% at 10 and 12 years; for the 70- to 79-year-old group, 69.6% ± 7.8% at 10 years; and for the group 80 years old and older, 56.4% ± 23.6% at 8 and 10 years. This assessment considers patients who died of valve-related complications or had residual neurological deficits from thromboembolism, antithromboembolic therapy–related hemorrhage, or prosthetic valve endocarditis. The hazard rates indicate the mortality and residual morbidity occurrence rates. The freedom from valve-related death, residual morbidity, and reoperation was 61.7% ± 7.0% at 10 and 12 years (see Fig 16). The freedom for the 65- to 69-year-old group was 60.5% ± 9.7% at 10 and 12 years; for the 70- to 79-year-old group, 67.4% ± 7.6% at 10 years; and for the group 80 years old and older, 56.4% ± 23.6% at 8 and 10 years. The hazard linearized occurrence rates indicate an increasing incidence throughout the observation period.

Table 17. Linearized Occurrence Rates of Valve-Related Complications by Valve Replaced[a]

Morbidity, Mortality	Type of Valve Replacement Aortic	Mitral	Multiple	Overall
Thromboembolism				
Overall	54 (2.3)	36 (2.6)	2 (0.9)	92 (2.3)
Fatal	13 (0.6)	8 (0.6)	1 (0.5)	22 (0.6)
Antithromboembolic therapy–related hemorrhage				
Overall	6 (0.3)	14 (1.0)	3 (1.4)	23 (0.6
Fatal	2 (0.09)	3 (0.2)	0	5 (0.1)
Clinical valve dysfunction				
Overall	4 (0.2)	6 (0.4)	0	10 (0.3)
Fatal	1 (0.04)	0	0	1 (0.03)
Prosthetic valve endocarditis				
Overall	5 (0.2)	4 (0.3)	2 (0.9)	11 (0.3)
Fatal	4 (0.2)	1 (0.07)	1 (0.5)	6 (0.2)
Paraprosthetic leak				
Overall	4 (0.2)	7 (0.5)	1 (0.5)	12 (0.3)
Fatal	1 (0.04)	2 (0.1)	0	3 (0.08)
Structural valve deterioration				
Overall	1 (0.04)	13 (0.9)	1 (0.5)	15 (0.4)
Fatal	0	3 (0.2)	0	3 (0.08)
Reoperation				
Overall	8 (0.3)	22 (1.6)	3 (1.4)	33 (0.8)
Fatal	3 (0.1)	3 (0.2)	1 (0.5)	7 (0.2)

[a] Data in parentheses are percent per patient-year, or episodes per 100 patient-years.

Table 18. Thromboembolism by Age[a]

Morbidity, Mortality	Age (yr)			
	65–69	70–79	≥80	Overall
Minor				
Overall	12 (0.7)	16 (0.8)	0	28 (0.7)
Major				
Overall	22 (1.2)	39 (2.0)	3 (2.3)	64 (1.6)
Fatal	6 (0.3)	14 (0.7)	2 (1.6)	22 (0.6)

[a] Data in parentheses are percent per patient-year or episodes per 100 patient-years.

The preoperative and postoperative New York Heart Association functional classification is shown in Figure 17. Preoperatively, 92.3% of the patients were in either class III or IV, whereas postoperatively, 93.0% were in class I or II.

The overall experience is summarized in Tables 20 through 23. The causes of the 33 reoperations are shown in Table 20 and the causes of the valve-related deaths (7 early and 33 late), in Table 21. The freedom from each valve-related complication and composites of complications are summarized in Tables 22 and 23.

Comment

The majority of reports on valve replacement have dealt with the safety of the procedure and the general quality of life of patients following valve procedures [1–29]. There has been limited documentation of valve-related complications in the elderly population [17]. In previous reports, we [14, 15] recommended that indications for valve replacement in the elderly be similar to those for the general population and that advanced age alone not be a contraindication to surgical management.

The operative mortality in various series of elderly patients was summarized in 1981. During the 1960s, the operative mortality for all reported valve replacements ranged between 15.3% and 40% [1, 2, 6–13]. During the decade of the 1970s, the mortality fell to a range of 3.7% to 10.7% [3–5, 14, 15]. In the 1960s, the operative mortality for AVR ranged from 8.7% to 33%; for MVR, 12% to 37%; and for multiple-valve replacement, 15% to 75%. In the 1970s, the mortality range fell appreciably; for AVR, 0% to 16%; for MVR, 5.6% to 9%; and for multiple-valve replacement, 0% to 33%.

Table 19. Thromboembolism by Valve Replaced[a]

Morbidity, Mortality	Type of Valve Replacement			
	Aortic	Mitral	Multiple	Overall
Minor				
Overall	20 (0.9)	8 (0.6)	0	28 (0.7)
Major				
Overall	34 (1.5)	28 (2.0)	2 (0.9)	64 (1.6)
Fatal	13 (0.6)	8 (0.6)	1 (0.5)	22 (0.6)

[a] Data in parentheses are percent per patient-year or episodes per 100 patient-years.

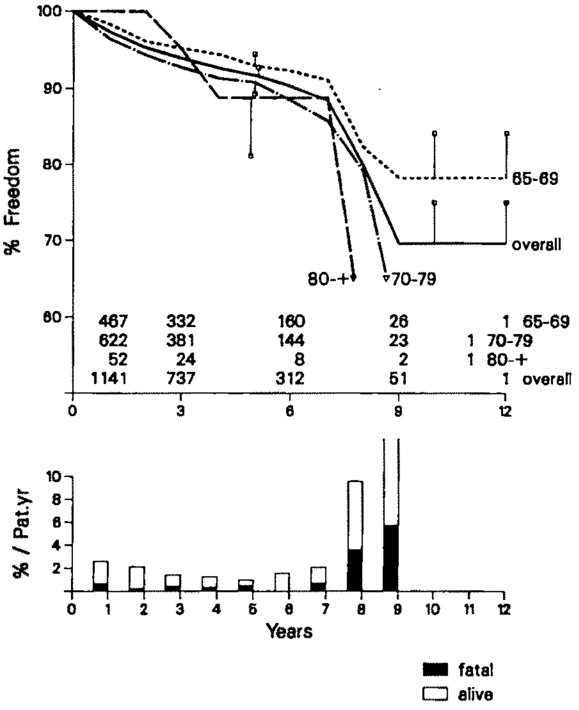

Fig 3. Freedom from thromboembolism by age.

The operative mortality we [15] reported for the 1970s was 8.8% overall and 4.7% for AVR, 11.4% for MVR, and 37.5% for multiple-valve replacement. The present series has some overlap with the previous series, for all operations with porcine bioprostheses from 1975 to 1987 are included. We know of no report that considers exclusively

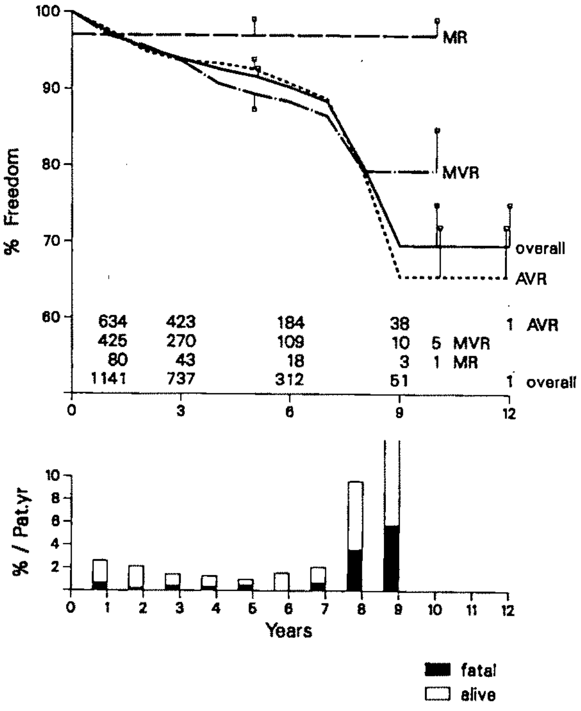

Fig 4. Freedom from thromboembolism by type of valve replacement. (AVR = aortic valve replacement; MR = multiple-valve replacement; MVR = mitral valve replacement.)

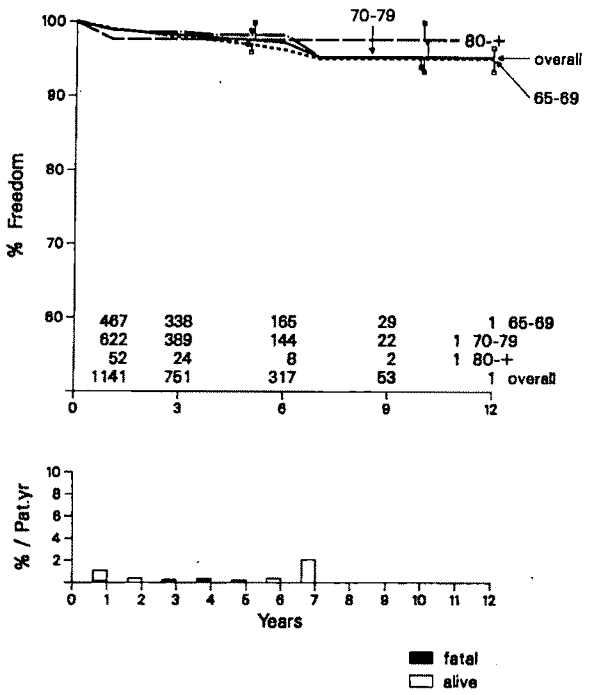

Fig 5. Freedom from hemorrhage related to antithromboembolic therapy.

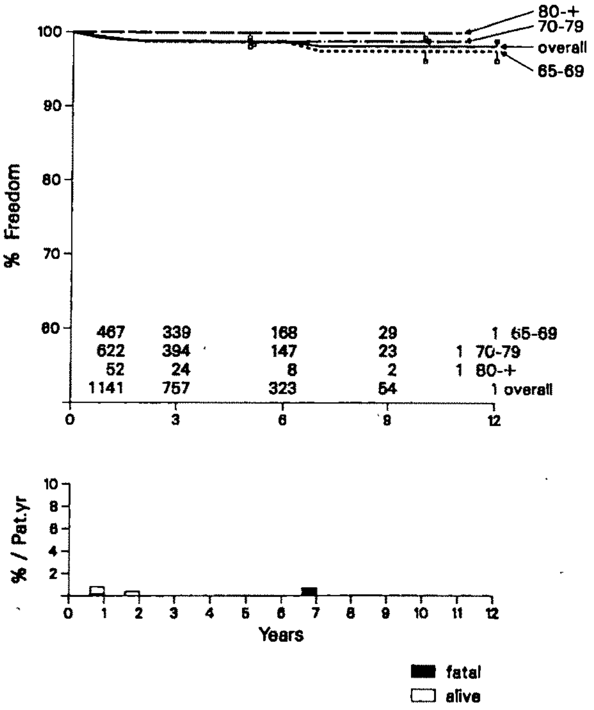

Fig 7. Freedom from paraprosthetic leak.

the mortality in the 1980s. Early mortality in the present overlapping series was 9.5% overall and 6.3% for AVR, 13.5% for MVR, and 13.8% for multiple-valve replacement. Only multiple-valve replacement showed improvement compared with our data for the 1970s. The series presented here included a substantial number of high-risk patients, for 46.6% had concomitant procedures and 10.1% had had previous cardiac operations. The mortality for valve replacements performed with concomitant procedures was 12.8% and for those without, 6.8%. The influence of previous procedures on mortality was also evident; 9.2% of patients without and 13.2% of those with such a procedure died early.

Another extensive series with a group of 360 patients

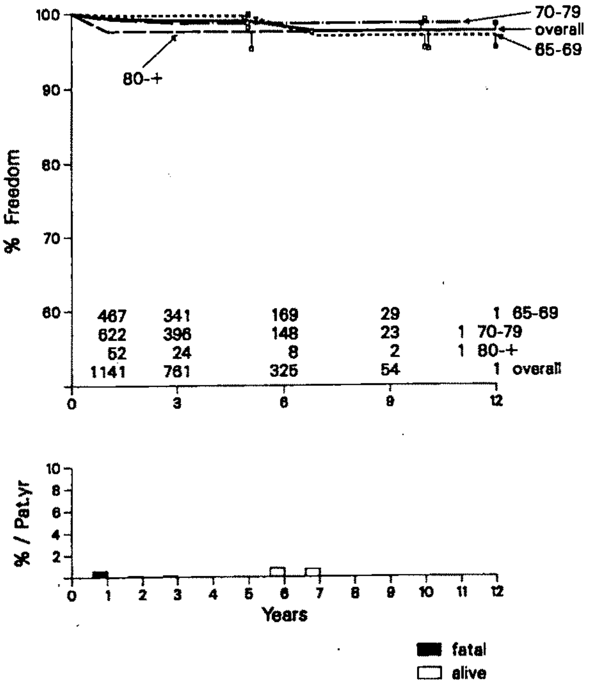

Fig 6. Freedom from prosthetic valve endocarditis.

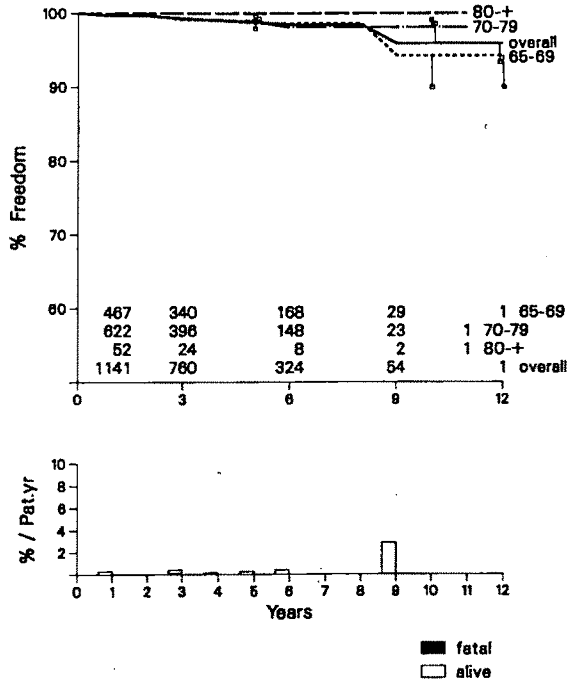

Fig 8. Freedom from clinical valve dysfunction.

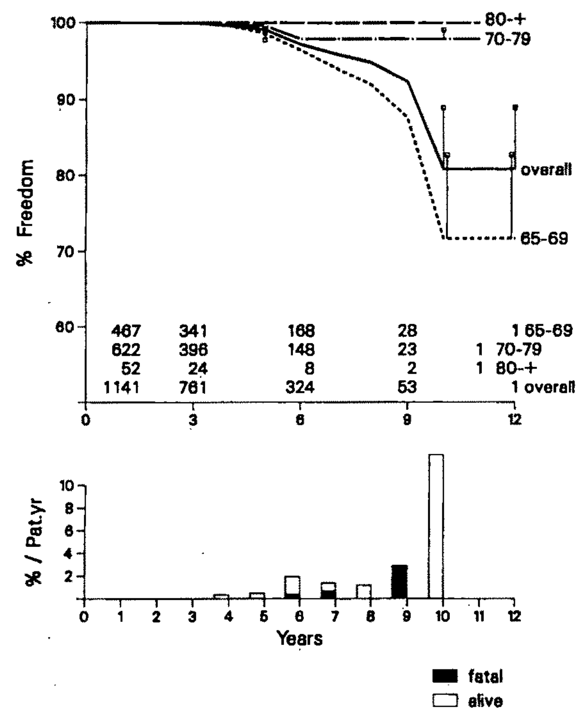

Fig 9. Freedom from structural valve deterioration by age.

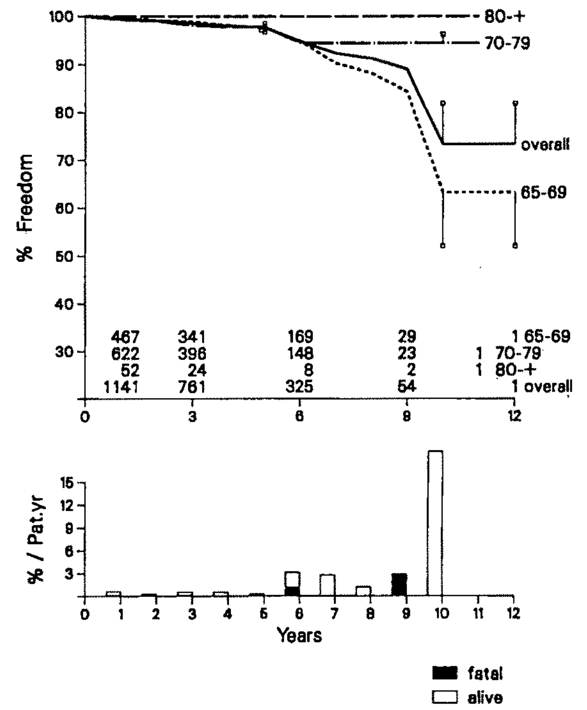

Fig 11. Freedom from reoperation.

older than 70 years is that reported by Bessone and colleagues [17] in 1985. This study revealed an early mortality of 11.5% for AVR, 15.7% for MVR, and 14.7% for multiple-valve replacement. In the present series, considering only patients 70 years of age and older, the overall early mortality was 11.1% (75/676 patients). In 1987, Blakeman and co-workers [18] reported only a 3% mortality among 100 patients 75 years of age and older undergoing isolated AVR. Craver and colleagues [20], in 1984, documented an early mortality of 5.1% for isolated AVR and of 5.4% for AVR and concomitant coronary

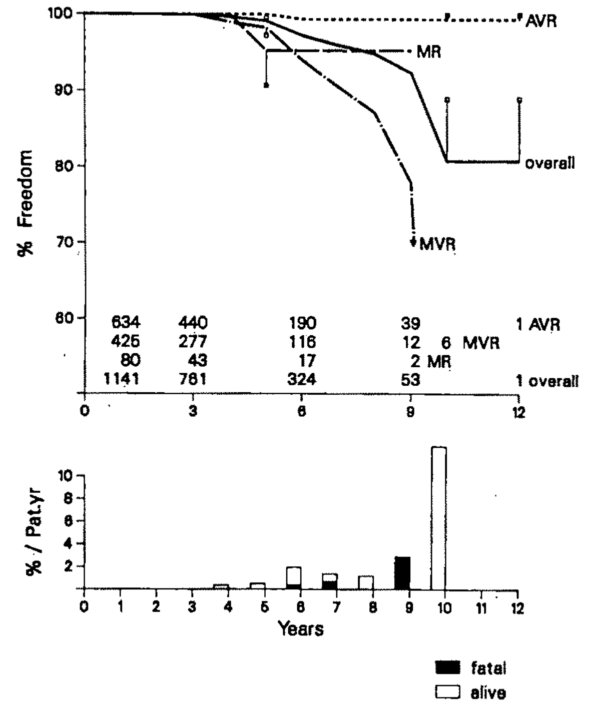

Fig 10. Freedom from structural valve deterioration by type of valve replacement. (AVR = aortic valve replacement; MR = multiple-valve replacement; MVR = mitral valve replacement.)

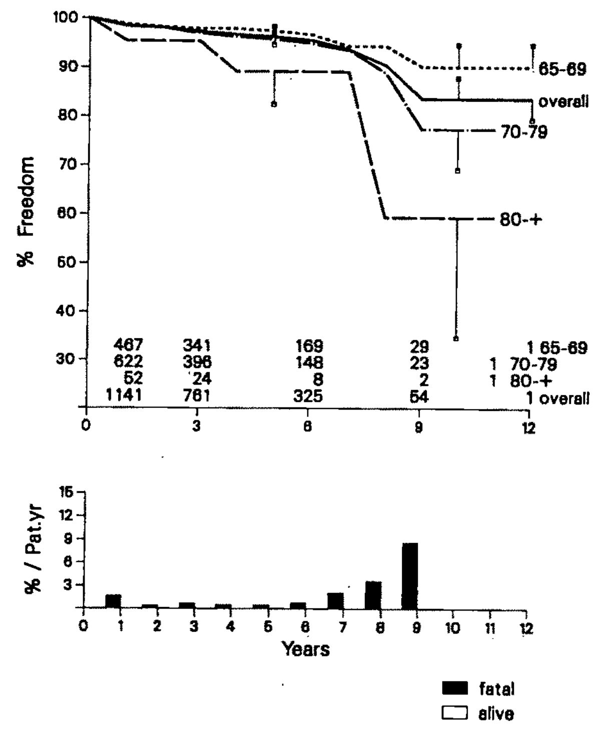

Fig 12. Freedom from valve-related death by age.

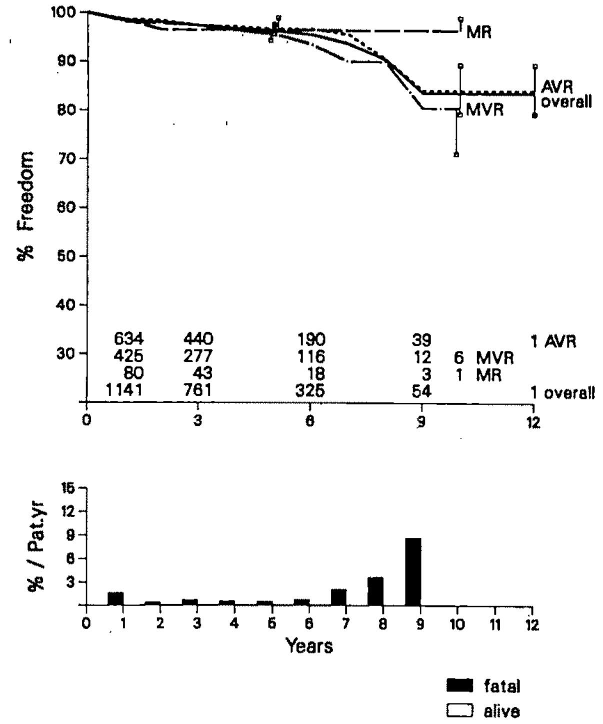

Fig 13. Freedom from valve-related death by type of valve replacement. (AVR = *aortic valve replacement;* MR = *multiple-valve replacement;* MVR = *mitral valve replacement.)*

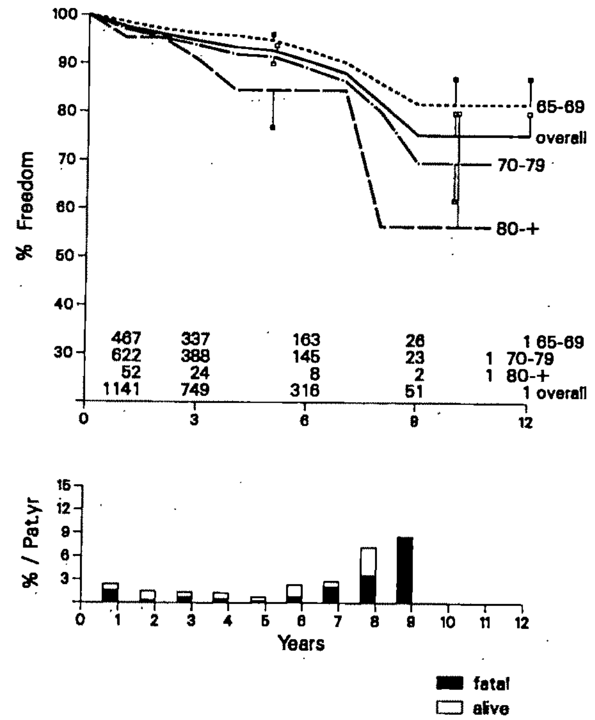

Fig 15. Freedom from valve-related death and residual morbidity (treatment failure).

artery bypass grafting in a series of 152 patients older than 70 years.

The late mortality is of considerable importance and was summarized in a previous study [15]. Late mortality has been as great as 9.1% per patient-year [13]. In the large series of Bessone and coauthors [17], late mortality was 7.6% per patient-year. In the present series, the rate was 5.5% per patient-year (AVR, 5.2% per patient-year; MVR, 6.2% per patient-year; and multiple-valve replacement, 5.4% per patient-year). By age group, late mortality

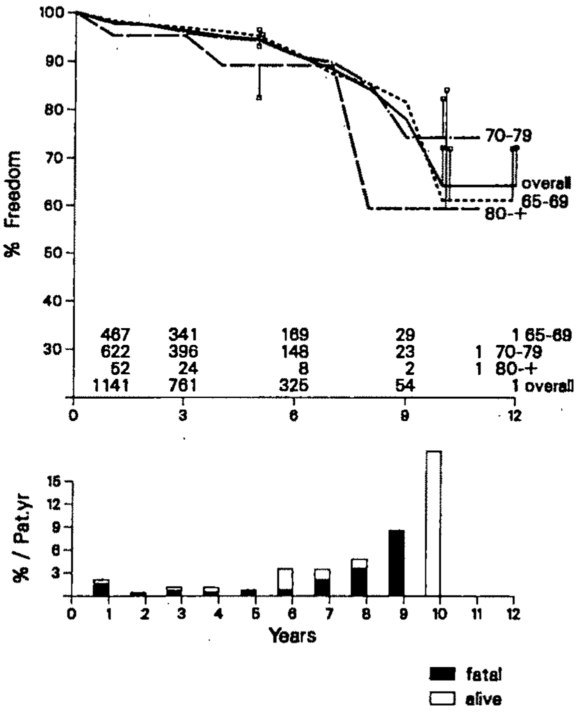

Fig 14. Freedom from valve-related death and reoperation.

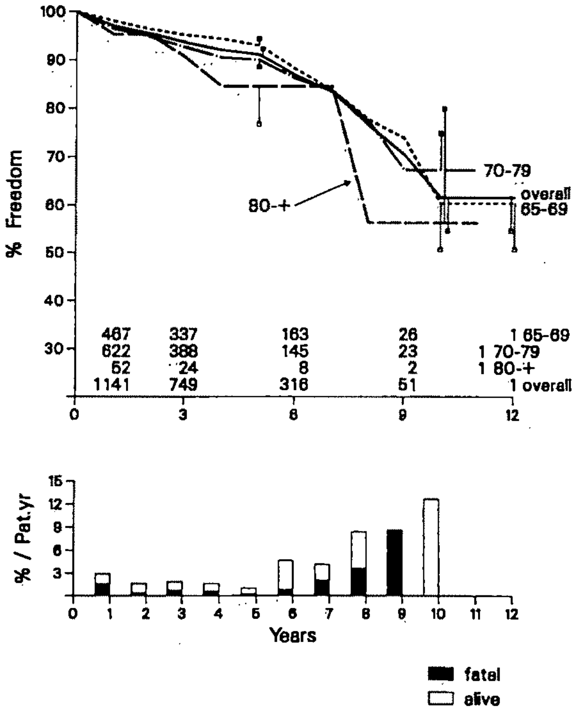

Fig 16. Freedom from valve-related mortality, residual morbidity, and reoperation.

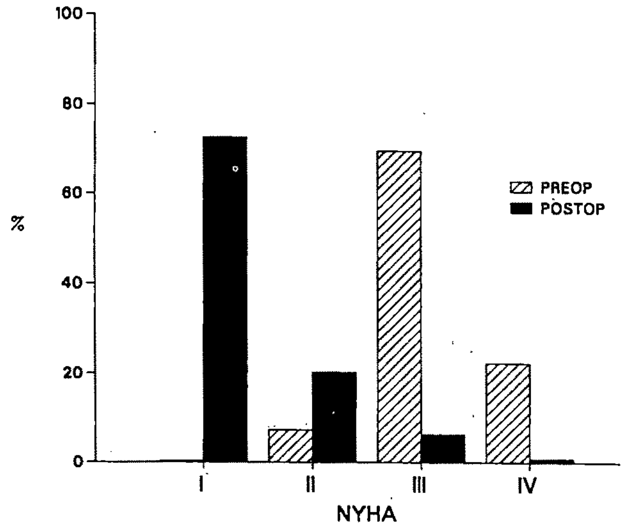

Fig 17. New York Heart Association (NYHA) *classification before and after operation.*

was 4.2% per patient-year for the group 65 to 69 years old, 6.3% per patient-year for the group 70 to 79 years old, and 14.1% per patient-year for the group 80 years old and older. The overall patient survival was 71% at 5 years and 48% at 10 and 12 years. Survival was 65% at 6 years in the series of Bessone and associates [17].

To our knowledge, this report provides the first overall assessment of valve-related complications of valve procedures in an elderly population. The freedom from all valve-related complications (including thromboembolism, hemorrhage related to antithromboembolic therapy, prosthetic valve endocarditis, paraprosthetic leak, and structural valve deterioration) at 10 and 12 years was 52%. At 10 and 12 years, the freedom from thromboembolism was 70% and from structural valve deterioration, 81% , while the freedom from all other complications was greater than 95%. Thromboembolic events increased with time, thus indicating other possible causes of thromboembolism attributed to the prostheses without detailed investigation.

Structural valve deterioration requires special consideration. The overall freedom from this complication at 10 and 12 years was 80.8%. There was a substantial difference in the age groups: 71.7% for the 65- to 69-year-old group at 10 and 12 years, 97.9% for the 70- to 79-year-old group at 10 years, and 100% for the group 80 years old or older at 12 years. This information illustrates the considerable safety of porcine bioprostheses for patients older than 70 years. The performance of the aortic prostheses was superior to that of the mitral prostheses both for MVR and multiple-valve replacement. Moront and Katz [30] reported calcification of a mitral prosthesis in a 72-year-old woman on a regimen of calcium carbonate therapy.

The overall performance of the porcine bioprostheses is best illustrated by considering the multiple decrement analysis of the complications. The freedom from reoperation, for all complications, was 73.3% at 10 and 12 years and was greater in patients 70 years old or older compared with those less than 70 years of age, thus reflecting the influence of structural valve deterioration. The overall freedom from valve-related death was 83.7% at 10 and 12

Table 20. Causes of Valve-Related Reoperation

Complication	Total
Thromboembolism	1
Antithromboembolic therapy–related hemorrhage	0
Clinical valve dysfunction	3
Prosthetic valve endocarditis	4
Paraprosthetic leak	10
Structural valve deterioration	15
Total	33[a]

[a] This total accounts for all the reoperations.

Table 21. Causes of Valve-Related Death

Complication	Early	Late	Total
Thromboembolism	3	19	22
Antithromboembolic therapy–related hemorrhage	1	4	5
Clinical valve dysfunction	0	1	1
Prosthetic valve endocarditis	1	5	6
Paraprosthetic leak	2	1	3
Structural valve deterioration	0	3	3
Total[a]	7 (109)	33 (219)	40 (328)

[a] Numbers in parentheses are the total number of deaths.

Table 22. Freedom From Valve-Related Complications[a]

Complication	5 Years	10 Years	12 Years
Thromboembolism	91.8 ± 1.0	69.6 ± 5.2	69.6 ± 5.2
Antithromboembolic therapy–related hemorrhage	97.6 ± 0.6	95.3 ± 1.3	95.3 ± 1.3
Clinical valve dysfunction	98.8 ± 0.4	95.9 ± 2.6	95.9 ± 2.6
Prosthetic valve endocarditis	99.1 ± 0.3	97.7 ± 0.9	97.7 ± 0.9
Paraprosthetic leak	98.8 ± 0.4	98.2 ± 0.7	98.2 ± 0.7
Structural valve deterioration	99.1 ± 0.4	80.8 ± 8.1	80.8 ± 8.1
Reoperation	97.8 ± 0.6	73.3 ± 8.6	73.3 ± 8.6

[a] Data are shown as the percent freedom ± the standard error.

Table 23. Freedom From Valve-Related Composite Complications[a]

Complication	5 Years	10 Years	12 Years
Valve-related death and reoperation	94.6 ± 0.9	64.3 ± 8.0	64.3 ± 8.0
Valve-related death	96.3 ± 0.7	83.7 ± 4.3	83.7 ± 4.3
Treatment failure	92.8 ± 1.0	75.4 ± 4.5	75.4 ± 4.5
Valve-related death, residual morbidity, and reoperation	91.3 ± 1.1	61.7 ± 7.0	61.7 ± 7.0
All valve-related complications	86.7 ± 1.3	52.1 ± 6.1	52.1 ± 6.1

[a] Data are shown as the percent freedom ± the standard error.

years; the age influence was reversed with the greater freedom in patients younger than 70 years of age, thereby reflecting the late mortality from thromboembolism in the older age groups (70 years old and more). The freedom from valve-related death and reoperation was 64.3% at 10 and 12 years, while the freedom from valve-related death and residual morbidity was 75.4%. Residual morbidity is defined as permanent neurological deficit from thromboembolism, hemorrhage due to antithromboembolic-related therapy, and embolic complications of prosthetic valve endocarditis. The most important index of performance is the 61.7% freedom from the combination of valve-related death, residual morbidity, and reoperation at 10 and 12 years.

The porcine bioprostheses provide excellent clinical performance in the elderly. The risk of structural valve deterioration (primary tissue failure) is low and essentially negligible at 10 and 12 years in patients older than 70 years.

We are indebted to our colleagues Dr G. F. O. Tyers, Dr M. T. Janusz, Dr H. Ling, Dr P. Allen, Dr H. Tutassaura, and Dr R. I. Hayden for allowing the inclusion of their patients in this study. We extend appreciation to Eva Germann, computer programmer, and Joan MacNab and Florence Chan for their extensive efforts in the preparation of this work.

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DISCUSSION

DR CONRAD L. PELLETIER (Montreal, Que, Canada): Dr Jamieson is to be complimented for this very timely and well-presented study. These data are important in two respects. First, they are important in regard to the target population. Elderly patients represent a growing proportion of patients undergoing valve replacement. It is therefore important to assess the risk/benefit ratio of this operation in this group of patients. Dr Jamieson has shown that early mortality increases with age, noncardiac-related causes being responsible for 25% of those deaths. We reported similar findings in a study published a couple of years ago, and stressed the need for careful patient selection to decrease noncardiac-related mortality and morbidity. In addition, the percentage of operative deaths is doubled when associated procedures are performed. I ask Dr Jamieson to comment on his approach to associated coronary lesions. Are all stenoses bypassed or only life-threatening ones? Also, what proportion of patients do associated coronary procedures represent in this series?

Second and mainly, these data are important in terms of the choice of the proper valve prosthesis for this age group. This study comes at a time when the use of bioprostheses is becoming somewhat more selective. We, like others, have changed our attitude regarding the choice of prosthesis. Bioprostheses represented more than 90% of our total valve implants in 1979 and slightly less than 50% in 1987.

The results reported by Dr Jamieson indicate that the elderly patient is well suited for placement of a bioprosthesis, not only because of the limited life expectancy, but more so because valve durability appears excellent up to 10 years in this age group, thus permitting us to avoid anticoagulants. However, I noticed that there was a higher incidence of thromboembolic complications in older patients. This may be at least in part related to the higher prevalence of atherosclerotic cerebral vessel disease with advanced age. Or could it be due to the absence of anticoagulation, even in patients with risk factors?

My second question therefore addresses the problem of anticoagulation, both during the early postoperative period and during long-term follow-up. Finally, what proportion of your patients was kept permanently on a regimen of anticoagulation therapy?

Again, I congratulate Dr Jamieson and his colleagues for their excellent and well-documented study.

DR CARY W. AKINS (Boston, MA): I congratulate Dr Jamieson on his usual excellent statistical assessment of a large series of patients. I do have one question, however.

If you define structural valve deterioration as that determined only at reoperation or autopsy, did patients more than 80 years old actually undergo reoperation as their valves began to deteriorate or were they merely allowed to die? The survival rate for the group 80 years old and more was obviously much lower. The question is, have you somewhat confused the issue, and is your conclusion that patients older than 80 years have little valve deterioration actually valid?

DR J. EDWARD OKIES (Portland, OR): I have a question about the size limitation of the prosthesis. Some elderly patients have a very small annulus. What is the lower size limit of tissue valve that you would place, and do you perform any reconstruction of the annulus to allow use of a bigger valve?

DR JAMIESON: I thank the discussants for their comments and questions.

Dr Pelletier, in regard to your question on coronary artery bypass, we performed concomitant procedures (approximately 95% for coronary artery disease) in 525 of our 1,127 patients. Coronary artery bypass was performed for hemodynamically significant lesions, up to three per patient.

The older patients, those 70 years of age or more, had a higher incidence of thromboembolism. The higher incidence may reflect an increased incidence of extracranial cerebrovascular disease. The patients were not generally investigated to determine the presence or absence of such disease. Thromboembolic events were considered valve-related if there were no known precipitating factors. Long-term anticoagulation is used after MVR in patients with chronic atrial fibrillation. Patients with AVR and MVR who are in sinus rhythm are generally not maintained with long-term anticoagulation.

Dr Akins, your comments regarding the patient group 80 years old and older are certainly well taken. The freedom from structural valve degeneration and reoperation is exceptional. There were 52 patients in this group, and 8 early deaths and 18 late deaths. To our knowledge, patients have not been refused reoperation. The patient interviews did not reveal mention, proposal, or refusal of reoperation. It remains possible that family physicians or cardiologists did not give consideration to reoperation for valve-related complications.

Dr Okies, the patients in this study were managed without aortic root enlargement. Aortic root enlargement is generally not performed in our institutions. In the majority of patients, the aortic valve size is not smaller than 21 mm. A 19-mm aortic valve is occasionally placed in low-weight women with limitation of activity level. We previously evaluated functional class by valve size, and found no correlation.

Internal Mammary Artery Bypass Grafting: Influence on Recurrent Angina and Survival in 2,100 Patients

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Internal mammary artery (IMA) bypass grafting to the anterior descending coronary artery was performed in 2,100 patients between January 1978 and July 1986. The average number of additional saphenous vein grafts (SVGs) per patient was 1.8. During the same period, 1,753 patients underwent coronary artery bypass grafting using an SVG (average number of grafts per patient, 3.2). The average patient age was similar: 62.3 years for IMA grafts and 64.7 years for SVGs. Men constituted two thirds of each group. Left ventricular function was impaired (ejection fraction <45%) in 1,071 (51%) of IMA grafts and 847 (48.3%) of SVGs. Other aggregate risk factors, ie, elevated blood pressure, diabetes mellitus, previous myocardial infarction, and congestive heart failure, were similar in each group. Operative results and postoperative mortality of the IMA and SVG patients were comparable. However, the long-term probability of cumulative survival and occlusion-free survival were significantly greater and the probability of recurrent angina and reoperative coronary artery bypass grafting were significantly less in IMA graft patients ($p < 0.015$). The relative risk of occlusion in an SVG was 4 to 5 times greater than that of the IMA graft. These data indicate that a patent IMA graft to the anterior descending coronary artery protects against recurrent angina and death from cardiac-related causes, and that the IMA should be the conduit of choice.

(Ann Thorac Surg 1989;48:186–91)

There is increasing evidence that patients who receive one or more internal mammary artery (IMA) grafts have improved long-term survival, decreased incidence of recurrent angina, and fewer late cardiac-related events [1–8]. This historical prospective study was undertaken to compare the long-term patency, survival, and incidence of recurrent cardiac symptoms in patients who received an IMA graft to the left anterior descending coronary artery (LAD) as compared with patients who received a saphenous vein graft (SVG) to the LAD in addition to other bypass grafts.

Material and Methods

All patients who have undergone open heart operations at St Vincent's Hospital and Medical Center, New York, New York, since January 1978 and at Maimonides Medical Center, Brooklyn, New York, since July 1982 have been entered into a computerized cardiac surgical data base. The data on patients who underwent isolated coronary artery bypass grafting with a graft to the LAD were analyzed. Patients who did not receive grafts to the LAD or who had multiple IMA grafts, reoperative coronary artery bypass grafting, or combined valve replacement with coronary artery bypass grafting were excluded from the study. Also, patients who required emergency coronary artery bypass grafting for cardiogenic shock, acute evolving myocardial infarction, or failed percutaneous transluminal coronary angioplasty were excluded from the study. A total of 3,853 patients who underwent coronary artery bypass grafting with a graft to the LAD during this time were entered into the study; 2,100 patients received an IMA graft to the LAD, and 1,753 patients received an SVG to the LAD.

Preoperative evaluation included history of diabetes mellitus, hypertension, previous myocardial infarction, congestive heart failure, smoking, renal failure, and hypercholesterolemia, and family history of heart disease. Myocardial infarction was defined as electrocardiographic presence of a Q wave that was greater than or equal to 3 mm in depth and greater than or equal to 0.4 seconds.

Cardiac Catheterization

Cardiac catheterization was performed on all patients, and included right heart catheterization with determination of cardiac output with a thermodilution or Fick technique. Left ventricular pressures were measured with a catheter inserted into the left ventricle before coronary angiography was performed. Ejection fraction was measured by a single-plane exposure by the area-length method or by gated blood pool scan.

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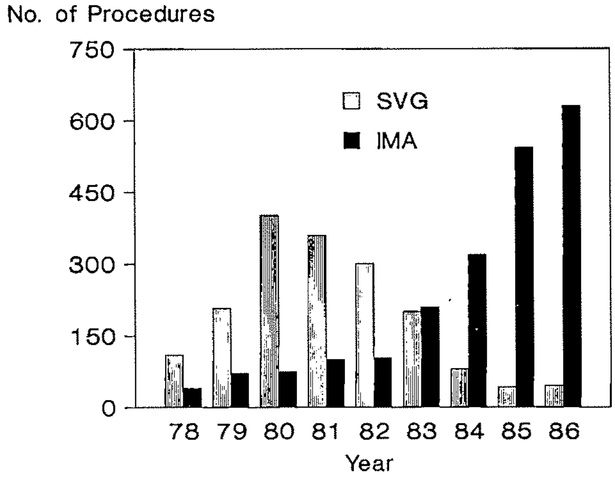

Fig 1. Frequency of internal mammary artery graft versus saphenous vein graft.

Coronary artery stenosis was considered clinically significant if there was at least a 70% or greater stenosis in the luminal diameter in any view. A stenosis of 50% or more in the left main coronary artery was considered clinically significant.

Operative Technique

All patients had pulmonary artery thermodilution catheters inserted before induction of anesthetia. Surgical techniques consisted of a standard median sternotomy with simultaneous removal of saphenous veins alone or combined with use of an IMA. Standard cardiopulmonary bypass, using either a bubble or membrane oxygenator, was employed in all patients. Myocardial protection was provided with multidose blood (hematocrit, 15% to 20%) potassium (30 mEq/L) cardioplegia combined with topical hypothermia. All distal anastomoses were constructed during a single period of aortic occlusion, and proximal anastomoses were constructed after removal of the aortic cross-clamp during rewarming. Inotropic pharmacological support or mechanical cardiac support, or both, was used when clinically indicated. Postoperative respiratory failure was defined as a patient requiring ventilatory support for more than 48 hours, and low cardiac output was defined as a patient requiring inotropic pharmacological support to maintain a cardiac index greater than 2.0 L/min/m^2 for more than six hours postoperatively.

The decision to use the left IMA for grafting to the LAD was made at the discretion of the operating surgeon. The IMA, used infrequently before 1982, is now used in almost all patients (Fig 1).

Repeat cardiac catheterization was performed at the discretion of the referring cardiologist and was generally performed for recurrent symptoms or simply to assess the patency of the grafts. All patients were contacted annually for follow-up by nurse-clinicians. Data in this paper include follow-up to January 1, 1987.

Statistical Methods

The probabilities of recurrent angina, reoperation, and late death were estimated using the large-sample actuarial method. Statistical significance was assessed by the Lee-Desu statistic with the computations performed by the SPSS package [9]. The frequency of occlusion of IMA grafts and SVGs was compared by using graft years of observation as the unit of measurement. This approach accounts for both the varying number of grafts per patient and the varying periods of follow-up. Statistical significance was assessed using a normal approximation to the binomial distribution [10].

The probabilities of occlusion in patients with IMA grafts and SVGs were estimated by drawing random samples of 100 patients with each procedure, selected so that a comparable number of patients with each type of bypass graft was included for each year from 1978 to 1982. The sample was not extended beyond this point because relatively few SVGs were performed after this time. The probability of occlusion was limited to occlusions occurring in the LAD for both types of bypass graft. Analysis of differences in the probability of occlusion was performed using the Kaplan-Meier estimate, an estimate of the cumulative probability of occlusion-free survival that decreases at each exact failure time. The estimated occlusion time was taken as one half of the interval during which the patient was last observed to be occlusion-free and the date of the examination when the occlusion was detected.

Differences in the probability of occlusion by type of operation were assessed by the log-rank test. Three versions were used offering different weighing schemes. The Mantel-Haenszel test gives equal weight to each failure; the Breslow-Gehen weights each failure by the total number at risk at the time failure occurs, resulting in accordance of greater weight to earlier times. The Tarone-Ware version weights by the square root of the total number at risk, which also places less weight on later failure times [11]. The actual computations were performed using Systat [12]. Other statistical procedures used included Student's t test, χ^2, and Fisher's exact test. When multiple testing was done, Bonferroni's inequality was used to adjust for multiple-comparison bias [13].

Results

Clinical and Angiographic Features

Table 1 summarizes preoperative clinical data. There was no significant difference between sex and preoperative clinical characteristics of patients receiving an IMA graft versus those receiving an SVG when adjustment was made for multiple-comparison bias. The percentage of patients with left main disease and abnormal ventricular function was also similar in both groups of patients. There was a significant difference in the average ages; the IMA group was 2.4 years younger than the SVG group, but this difference did not appear to be biologically important because, on the average, both groups were aged approximately 60 to 65 years.

Operative Results

Operative results are summarized in Table 2. The mean number of grafts performed in both groups of patients was similar, as was operative mortality. The postoperative

Table 1. Preoperative Clinical and Angiographic Data[a]

Variable	IMA Graft	SVG	*p* Value
Total No. of patients	2,100	1,753	
Men	1,428 (68.0)	1,157 (66.0)	NS
Women	672 (32)	596 (34.0)	NS
Mean age (yr)	62.3 ± 17.9	64.7 ± 19.2	<0.01
Age range (yr)	36–79	42–82	
Hypertension	793 (37.7)	718 (40.9)	NS
Diabetes mellitus	387 (18.4)	370 (21.1)	NS
Previous myocardial infarction	1,121 (53.4)	981 (56.0)	NS
Congestive heart failure	253 (12.0)	193 (11.0)	NS
Left main disease	401 (19.1)	378 (21.0)	NS
Ejection fraction <45%	1,071 (51.0)	847 (48.3)	NS

[a] Numbers in parentheses are percentages.

IMA = internal mammary artery; NS = not significant; SVG = saphenous vein graft.

complication rate and mortality rate were also similar in both groups.

Follow-up Cardiac Catheterization

A total of 627 patients or 29.8% of the 2,100 patients with IMA grafts underwent follow-up catheterization (Table 3). The 2,100 patients with IMA grafts were followed for 6,121 patient-years, yielding a catheterization rate of 10.2/100 years. This was twice the rate of catheterization (555/10,316, or 5.4/100) for the 1,753 patients undergoing coronary artery bypass grafting with SVGs ($p < 0.001$) (Table 4). Among the 2,100 patients with IMA grafts, the rate of occlusion of the IMA was 4.1/1,000 patient-graft years versus 19.9 for the SVG in these same patients. The risk of occlusion was 4.9 times higher in the SVG than the IMA graft in a given patient (95% confidence interval [CI], 3.2 to 7.4). In the 1,753 patients with only SVGs, the rate of occlusion was 17.1/1,000 graft years of observation, which did not differ significantly from the earlier noted rate of SVG occlusion (relative risk, 0.86; 95% CI, 0.74 to 1.002). Again, SVG patients had a significantly higher risk of occlusion compared with IMA patients (relative risk, 4.1; 95% CI, 2.75 to 6.18).

Table 2. Operative Results and Postoperative Mortality[a]

Variable	IMA Graft	SVG
Mean No. of grafts	2.8 ± 1.1	3.1 ± 1.0
Deaths	34 (1.6)	30 (1.7)
Reoperation for bleeding	23 (1.1)	23 (1.3)
Perioperative myocardial infarction	43 (2.0)	39 (2.2)
Mediastinitis	22 (1.0)	16 (0.9)
Respiratory failure	45 (2.1)	35 (2.0)
Cerebrovascular accident	24 (1.1)	23 (1.3)

[a] Numbers in parentheses are percentages. There were no significant differences between the IMA and SVG groups.

IMA = internal mammary artery; SVG = saphenous vein graft.

Table 3. Follow-up Cardiac Catheterization for IMA Graft Patients

Year	Patients	IMA Coronary Angiography	Patent IMA No.	Patent IMA %	Patent SVG (%)
1978	41	30	28	93	78
1979	72	51	48	94	80
1980	75	46	43	94	79
1981	101	71	69	97	85
1982	105	89	87	98	79
1983	210	138	134	97	85
1984	320	100	96	96	86
1985	544	102	97	95	86
1986	632	0	. . .	. . .	. . .
Total	2,100	627	602	96	81

IMA = internal mammary artery; SVG = saphenous vein graft.

The likelihood of occlusion developing in the sample of 200 patients selected to minimize secular trends is shown in Fig 2. In the IMA patients, all occlusions occurred within 1 year of operation, yielding a cumulative probability of 14%; thereafter, no further occlusions developed. In the SVG group, the first occlusion occurred more than 2 years after operation. However, with time, the probability of occlusion in the SVG group increased: at 4 years, it exceeded the probability of occlusion in the IMA group, and it ultimately increased to 28% throughout the study period compared with 14% in the IMA group. The probability of developing an occlusion 4 years or more after operation was significantly greater in the SVG group ($p < 0.015$) by each of the log-rank tests.

Recurrent Symptoms and Late Mortality

The cumulative probability of developing recurrent angina was 30.6% in patients with SVGs alone up to 9 years

Table 4. Follow-up Cardiac Catheterization for SVG Patients

	Patients	SVG Coronary Angiography	Patent SVG
1978	110	60	45 (75)
1979	208	71	48 (67)
1980	402	202	95 (47)
1981	360	81	69 (85)
1982	302	64	55 (85)
1983	201	46	36 (78)
1984	84	31	28 (90)
1985	43	. . .	. . .
1986	46	. . .	. . .
Total	1,753	555	376 (68)

Numbers in parentheses are percentages.

SVG = saphenous vein graft.

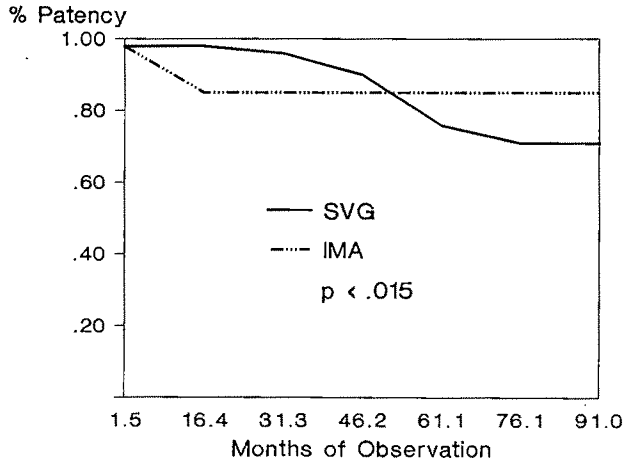

Fig 2. Cumulative incidence of occlusion-free survival in sample patients (n = 200).

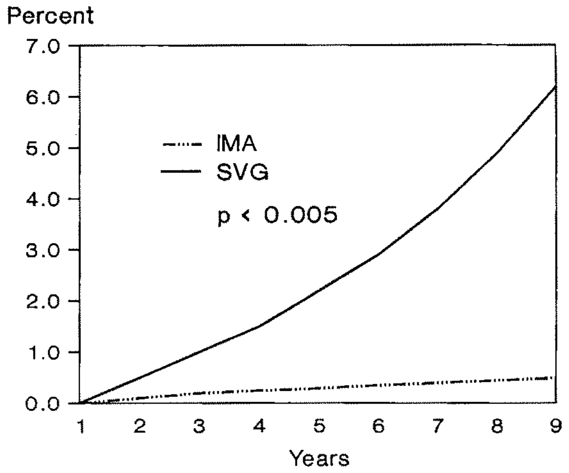

Fig 4. Incidence of reoperative coronary artery bypass grafting.

after operation compared with 18% of patients with IMA grafts (Fig 3, $p < 0.01$). The cumulative probability of reoperation either for recurrent symptoms or for compelling anatomy was 6.2% of patients with SVGs compared with 0.5% of patients with IMA grafts (Fig 4, $p < 0.005$). Cumulative mortality from all causes was 22.0% in patients with SVGs and 10.0% in patients with IMA grafts (Fig 5, $p < 0.01$).

Comment

Clearly this type of retrospective study has a number of limitations. First, patients were not prospectively randomized to receive an IMA graft rather than an SVG. Second, the difference in mean follow-up between patients who received an IMA graft compared with patients who received an SVG can lead to bias from secular trends. Third, not all patients have undergone repeat catheterization, nor did patients undergo repeat catheterization at similar time intervals. Finally, it was not possible to retrieve the data necessary to stratify patients for individual risk factors between IMA and SVG patients.

However, Table 1 shows in aggregate that risk factors were comparable among patients with IMA grafts and SVGs. The random samples of 100 patients with each procedure were selected so that equal numbers with each procedure were drawn from each year to reduce bias from secular trends. The results from the sample showed an increased probability of occlusion in SVG patients as length of follow-up increased. Furthermore, when graft years of exposure were used as the unit of measurement, the likelihood of occlusion in the SVG was 4 to 5 times greater than in the IMA. This is consistent with observations in other large studies that the IMA has better long-term patency than the SVG. In addition, patients who receive at least one IMA graft to the LAD have a lower incidence of recurrent symptoms; if symptoms do recur there is less likelihood of reoperation; and long-term survival appears to be better in patients who receive an IMA graft to the LAD [1, 4, 6, 8, 10–13].

Studies have shown (over a finite time) serial angiographic arteriosclerotic changes in SVGs, whereas the IMA usually remained angiographically normal [1, 5–8, 14–17]. The early changes in the saphenous vein have

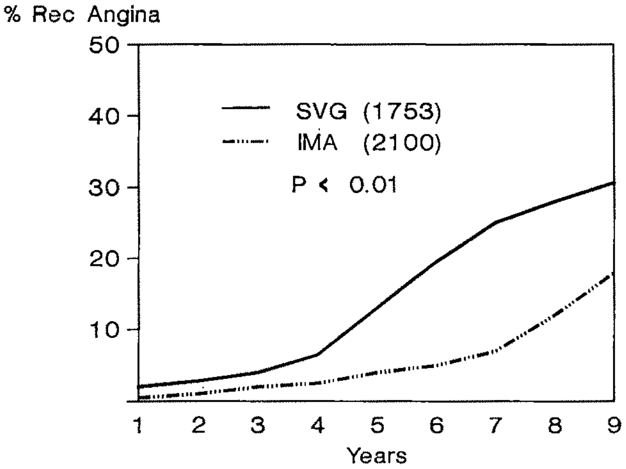

Fig 3. Cumulative probability of recurrent angina.

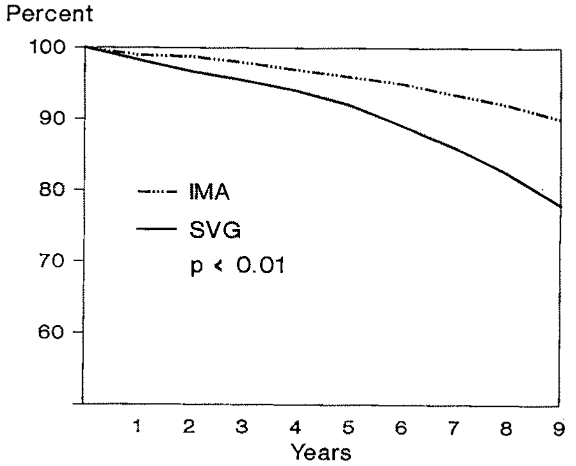

Fig 5. Cumulative total survival of patients with recurrent angina.

been postulated to occur as a result of platelet and fibrin deposition on injured vein graft intima [18]. This may promote medial muscle cell proliferation and intima and intimal hyperplasia. Later, the smooth muscle cells of the media may be replaced by fibrous tissue and lipoid material may be deposited on the intima. Thus, in time, the wall of the saphenous vein becomes thicker, with resultant luminal narrowing. The IMA, on the other hand, demonstrates little morphological change and maintains its luminal size over time [18].

Not all SVGs undergo these changes. Events that contribute to these changes may be related to intrinsic factors (eg, chronic phlebitis, varicosity, small diameter), extrinsic factors, (eg, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus), and technical factors (eg, kinking, pursestringing of the anastomosis, pericardial constriction) [8, 15, 17]. Whether pharmacological intervention with antiplatelet drugs or calcium channel blocking agents will effect long-term vein graft patency (greater than 5 years) has not yet been determined [19].

Why the IMA remains immune to arteriosclerotic changes is not completely clear. It has been suggested that this may be due in part to inherent vasoactive properties [20]. Experimental studies have shown that the IMA is capable of adapting its flow to vasoactive drugs (isoproterenol) [20] and can increase its flow sufficiently to supply a number of coronary arteries when a sequential anastomosis is performed [21].

The long-term patency we achieved with the IMA graft is consistent with findings in other large series [1–8]. Most occlusions occurred within the first year after the patient's bypass. In the sample series of 200 patients, most occlusions occurred early in our experience of IMA graft use. We believe that this indicates technical problems associated with the anastomosis and suggests the existence of a learning curve that has not been witnessed since the first year of this retrospective study.

In this study, as in other studies [5, 6, 8, 21–24] no increased incidence of complications was associated with dissection and use of the IMA. Clearly, as operating surgeons become more familiar with this procedure, it is less likely that complications will occur. Nevertheless, for some cohorts of patients (elderly, female, obese, diabetic) use of the IMA may pose an increased risk of postoperative morbidity. In some patients, the risk of using bilateral IMAs may also be higher.

In summary, this study and other studies clearly show that patients who receive in situ IMA grafts to the LAD have improved long-term survival, have fewer recurrent symptoms, and have fewer late cardiac-related events. In addition, patients in whom recurrent angina develops probably can be managed medically and will not require reoperation. Most likely, this is a result of the improved long-term patency of the IMA. Further study is required to determine the long-term efficacy of sequential artery grafting, bilateral mammary artery grafting, and free mammary artery grafting and also to determine which patients (if any) will be prone to increased morbidity with use of extended mammary artery grafting.

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DISCUSSION

DR NOEL L. MILLS (Jefferson, LA): I thank Dr Acinapura for the opportunity to review his manuscript describing a retrospective study on IMA graft versus SVG to the LAD.

Historically, a survey in 1976 by Miller revealed that only 6% of surgeons in the United States were using IMA grafts. Within about 5 years, his second survey showed that 13% of surgeons in the United States were using the IMAs. By 1985, almost 95% of surgeons in the United States were using the IMA almost routinely.

Dr Acinapura concludes from his study that patients who receive IMA grafts to the LAD have improved survival, fewer recurrent symptoms, and fewer late cardiac deaths. Although other data have indicated that these findings may be true, we must not conclude that they are true merely on the basis of this report.

In the first 4 years of this study, from 1978 to 1982, most of the grafts were SVGs to the LAD. Then, from 1982 to 1986, most of the grafts were IMA grafts to the LAD. Therefore, the SVG group had twice as long to develop symptoms, to die, and to incur cardiac-related events.

I'd like to congratulate Acinapura and associates on obtaining the impressive 30% and 32% recatheterization rates in the two patient groups, in view of the need for cost containment. These patients underwent recatheterization due to "recurrent symptoms" and "to assess the patency of the grafts."

Why was the recatheterization interval at a mean of 3.1 years in the IMA group and at a mean of almost 6 years in the SVG group? One would expect just the opposite if the IMAs were offering the protection suggested, as they had fewer years at risk; ie, most of them were in place only since 1982.

Finally, the mean number of grafts in both groups was three per patient. This is not far from the national average of about four grafts per patient for elective coronary artery bypass grafting in the United States between 1978 and 1982. However, a mean of three grafts per patient in the IMA group, most of whom underwent bypass grafting in the years between 1982 and 1986, is low, and may account for the almost 20% recurrence rate of angina in that group. This low figure may result from some incomplete revascularizations in times when patients are being referred with more advanced disease.

We all realize that we are beyond the point of randomizing LAD and IMA grafts prospectively. I have been a champion of the IMA graft since 1972, but I do think that when we interpret these data we must be careful in accepting the authors' conclusions.

The low operative mortality and postoperative morbidity rates attest to the excellence of the surgeons. I congratulate Dr Acinapura on his presentation.

DR ACINAPURA: I thank Dr Mills for his comments. In regard to the shorter time interval in obtaining angiograms in patients who have undergone IMA bypass grafting, a substantial number of these patients underwent elective coronary angiography 1 to 2 years postoperatively to assess patency. These patients, if they remained asymptomatic, were not restudied again. The other patients were mainly studied because of recurrent angina pectoris. The patency rate, regardless of the time, remained high, in the range of 95% to 96%, and the mean duration for follow-up angioplasty is, accordingly, less for this group of patients with IMA bypass grafts.

The mean number of bypass grafts is somewhat less than the national average, and I agree with Dr Mills' comment that this probably relates to the high incidence of recurrent anginal symptoms in some of our patients, which is probably the result of both incomplete revascularization and progression of the native coronary artery disease. We have been somewhat reluctant to bypass vessels smaller than 1.5 mm because if and when these vessels are bypassed, their long-term patency is certainly suspect.

Missiles in the Heart

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The records of 24 patients who had a missile retained in the heart and who were treated at Grady Memorial Hospital from 1968 to 1987 were reviewed. In 22, the missile lodged in the heart after its direct injury and in the remaining 2, after the bullet injured a systemic vein. Immediately after the cardiac injury, 7 of the 22 patients were seen with cardiac tamponade (3 also had hemothorax), 11 were seen with hemothorax, 5 were asymptomatic, and 1 was in shock. Seven patients underwent emergency thoracotomy; the bullet was removed in 3, but in the remaining 4 patients, it was not located. In the other 17 patients and in the 4 in whom the bullet could not be found during emergency thoracotomy, the diagnosis was suspected from the chest roentgenograms and confirmed by cardiac fluoroscopy or angiocardiography. Eight patients with retained bullets underwent elective operation; the bullet was removed from 7 and in 1 it was left embedded in the right ventricular septum. All 10 patients who underwent excision of the missile recovered without complication except 1 in whom pericarditis developed, and all were followed for up to 17 years. All 14 patients with a retained missile in the heart had no cardiac symptoms referable to the bullet and were followed for up to 15 years. This experience suggests that the management of patients with a bullet of .38 caliber or smaller that is retained in the heart should be individualized according to the patient's clinical course and the site of the bullet and that in select patients, bullets left in the heart are tolerated well.

(Ann Thorac Surg 1989;48:192–4)

The management of patients with a bullet in the heart remains controversial. To answer the questions whether or not all bullets in the heart should be removed and whether those that are not removed are tolerated over a long period, our experience at Grady Memorial Hospital was reviewed.

Material and Methods

During the 19-year period from 1968 to 1987, 24 patients with a bullet in the heart were treated at Grady Memorial Hospital. All of them were male, and age ranged from 16 to 54 years (mean age, 29 years). In 22 of the patients, the missile lodged in the heart after its direct injury. In the other 2, the bullet pierced and entered an iliac vein and subsequently migrated and became entrapped in the right ventricle. Eighteen of the retained missiles were bullets .38 caliber or smaller, one was a fragment of a bullet, and five were pellets (Table 1).

Table 1. Missiles Retained in the Heart and Their Management

Missile	Removed	Not Removed	Total
Bullet	9	9	18
Bullet fragment	1	0	1
Pellets	0	5	5
Total	10	14	24

Immediately after the injury, 7 patients were seen with cardiac tamponade (3 of whom also had hemothorax), 11 were seen with hemothorax, 5 were asymptomatic, and 1 was in shock. Eight patients had concomitant intraabdominal injuries, and 2 other patients had abdominal injury resulting only in a wound of the iliac vein. The initial management consisted of observation of the 5 asymptomatic patients and tube thoracostomy in the patients with hemothorax. Seven patients underwent emergency exploratory thoracotomy, 6 for cardiac tamponade (the seventh patient with tamponade responded to pericardiocentesis and operation was delayed for nine days) and 1 for continuous intrathoracic bleeding. The 8 patients with intraabdominal injury underwent exploratory laparotomy.

Results

In 3 of the 7 patients who underwent emergency thoracotomy, the missile was removed. Two of the missiles were bullets in the pericardial space, and one was a bullet fragment, which was excised from the left ventricular myocardium. In the other 4 patients, the bullets could not be removed safely; they were thought to be embedded in the right ventricle in 2 patients and in the left ventricle in 2.

The diagnosis of missile in the heart in the remaining 17 patients was suspected from the chest roentgenograms, which showed a bullet or pellets in the cardiac silhouette. This diagnosis was confirmed by angiocardiography in 12

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patients and by cardiac fluoroscopy in 5. The 4 patients who underwent emergency thoracotomy without removal of the bullet subsequently underwent angiocardiography for localization of the missile.

Seven of the 21 patients with a retained missile in the heart underwent elective operation without cardiopulmonary bypass, and the bullet was removed. One other patient was operated on with the use of cardiopulmonary bypass, but the bullet could not be removed safely because it was completely embedded high in the ventricular septum behind the tricuspid valve. In the remaining 13 patients, no attempt was made to retrieve the missile.

Therefore, 10 of the 24 patients, 9 with a bullet and 1 with a bullet fragment, had excision of the missile (see Table 1). The missiles were extracted for several reasons. In 3 patients, the missile was easily accessible at the time of emergency thoracotomy for cardiac tamponade. The bullet was removed in 3 patients because of fear of its subsequent embolization, thrombus formation with embolization, or subsequent development of bacterial endocarditis. In 2 of these patients the bullet was partially protruding into the left ventricular cavity, and in the other, the bullet was in the right inferior pulmonary vein at its junction with the left atrium. In 2 patients, 1 with a bullet adjacent to the main pulmonary artery and the other with a bullet near the ascending aorta, the missile was retrieved because of fear of subsequent erosion of these vessels. In the remaining 2 patients, both of whom had a bullet in the pericardial space, the missile was removed because of fear of subsequent pericarditis.

In 14 patients, 9 with a bullet and 5 with pellets, the missile was not removed (see Table 1). In 5 of these patients the missile was completely embedded in the right ventricular myocardium; in 3, in the left ventricular myocardium; and in 2, in the ventricular septum. In 2 other patients, the bullet was trapped in the right ventricular trabeculations following its migration from the iliac vein and in 2 more patients, the missile was in the pericardial space. These missiles were left in place because the patients did not want to be operated on, because the missile could not be safely removed, or because it was considered safe to leave the missile in place.

The 10 patients in whom the missiles were removed have been followed for 2 months to 17 years (mean follow-up, 4 years). The only complication in this group was the occurrence of postoperative pericarditis in 1 patient. The 14 patients in whom the cardiac missile was left in place have been followed from 2 months to 15 years (mean follow-up, 5 years; 4 have been followed for 10 years or more). All these patients were free from symptoms related to the missile. One patient died of alcoholic cardiomyopathy 17 months after injury (Table 2).

Comment

With the progressive increase in the use of guns as assault weapons, the number of patients seen with a bullet in the heart is expected to rise. Bullets usually reach the heart after a penetrating wound to the heart or, rarely, to a systemic vein [1]. After injury to the heart, most missiles are either embedded in another organ or leave the thoracic cavity. Occasionally, however, at the time of the cardiac injury the bullet becomes embedded in the myocardium or falls into a cardiac chamber or the pericardial space. During the 19-year period of this study, we treated 68 patients with a gunshot wound to the heart. In 22 of them, the missile was retained in the heart.

A missile in the heart can be free in a cardiac chamber, partially embedded in the cardiac muscle and partially protruding into a cardiac chamber, or completely embedded in the myocardium. The missile can also be floating free in the pericardial space.

Bullets free in the left cardiac chambers usually embolize into a systemic artery shortly after entering the chamber [2]. Bullets free in the right cardiac chambers, particularly the right ventricle, can embolize into the pulmonary vascular bed [1] or may remain entrapped in its trabeculations indefinitely after they become encysted with fibrous tissue [3]. Sometimes, when a right-to-left shunt is present at the atrial level, a missile in the right atrium can migrate into the left atrium and embolize into the systemic arteries.

Bullets can occasionally reach the right side of the heart following an injury to a systemic vein. After entering a systemic vein, the missile usually migrates to the heart and either occasionally becomes entrapped in the right ventricular trabeculations or frequently embolizes into the pulmonary arterial bed [1]. In 2 of our 24 patients, the bullet reached and remained in the heart after an injury to an iliac vein and intravascular migration of the missile to the right ventricle.

The immediate postinjury clinical manifestations of missiles in the heart are those produced by the cardiac wound, ie, cardiac tamponade or intrathoracic bleeding. Rarely, patients with a bullet in the heart can have symptoms of valvular incompetence, communication between the aorta and the heart or pulmonary artery, and intraventricular communication or conduction defects, or they can be free from symptoms.

The subsequent manifestations of missiles in the heart are dependent on the site, shape, and size. Patients with bullets, particularly bullets with smooth edges and less than 1 to 2 cm in two of their three dimensions, embedded in the myocardium are usually free from symptoms [3–8]. Patients with bullets sitting free in a cardiac chamber or partially protruding into it can be seen with symptoms and signs of systemic or pulmonary embolization of the missile or thrombi, or they can be seen with a clinical picture of bacterial endocarditis [5, 8, 9]. Patients with bullets in the pericardial space can be asymptomatic or occasionally they have symptoms and signs of pericarditis, usually nonsuppurative [3, 10].

Table 2. Results

Result	Missiles Removed	Missiles Not Removed
Asymptomatic	9	13
Postoperative pericarditis	1	0
Died of alcoholic cardiomyopathy	0	1

Patients with a missile in the heart can also have neurotic manifestations of various degrees and character [8, 11]. Often they complain of palpitation, or occasionally they have a sense of impending death, not unlike that found in patients with coronary heart disease [9]. Although our patients were not asked any specific questions to uncover neurotic manifestations and no psychological testing was done, none of our patients during follow-up described to an examining physician any specific neurotic symptoms related to the retained missile. Also none of the patients in whom the bullet was not removed had any special complaints that could be attributed to the bullet. In only 1 patient did pericarditis develop after the bullet was removed.

The diagnosis of missile in the heart or pericardial space should be suspected when a metallic foreign body is seen in the cardiac silhouette in the initial roentgenogram. The diagnosis should be established first by cardiac fluoroscopy, and then the site and the degree of the bullet's embedment into the myocardium should be confirmed by echocardiography, computed tomography, or angiocardiography [12, 13].

In conclusion, our limited experience suggests that the management of patients with a bullet of .38 caliber or smaller retained in the heart should be individualized. Bullets easily accessible at the time of emergency thoracotomy for cardiac tamponade or bleeding should be removed. When this is not possible, the site and the degree of the embedment of the bullet in the myocardium should be confirmed by echocardiography, computed tomography, or angiocardiography before management is decided.

Missiles causing any symptoms should be removed. Bullets that are .38 caliber or smaller and that are completely embedded in the myocardium appear to be well tolerated and can be left alone. Bullets partially or completely free in a left cardiac chamber should be removed to avoid systemic embolization of the bullet or clots or subsequent development of bacterial endocarditis. Bullets free in the right cardiac chambers should be allowed to embolize into the pulmonary artery where they can be retrieved without a cardiotomy. Two of our patients with a bullet trapped in the right ventricular trabeculations after migration through the systemic veins have had no problems from the bullet. Nevertheless, perhaps bullets trapped or partially protruding into a right cardiac chamber should be removed during the early postinjury period to protect the patient from the possible development of bacterial endocarditis. In an asymptomatic patient with a bullet that has been in a right cardiac chamber for a long time and in a patient with a bullet in the pericardial space, the bullet can be left alone.

Although most bullets can be found and removed at the time of an elective operation, occasionally this is not the case, as in 1 of our patients. Perhaps the use of other techniques intraoperatively to help precisely localize the bullet, such as ultrasonography [14], may be useful in these rare instances.

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Pleuroperitoneal Shunts in the Management of Persistent Chylothorax

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Between June 1981 and June 1988, we placed pleuroperitoneal shunts in 16 patients for the management of refractory chylothorax on the Pediatric Surgical Service, University of Virginia. The cause of the chylothorax was caval thrombosis from central venous catheters in 5 patients, idiopathic in 3, and mediastinal lymphangioma in 2, and in 6, it developed after a cardiac procedure. Chylothorax in each patient was unresponsive to thoracentesis, tube thoracostomy, and dietary manipulations. A Denver double-valved shunt system is currently employed and is implanted using general anesthesia. Manual pumping is required postoperatively for several months. Twelve (75%) of the 16 patients had excellent results with complete elimination of the chylothorax and resolution of symptoms. In 10 of these 12, the shunt has been removed. Four had an unsatisfactory result: 3 had inferior vena cava hypertension, and 3 were low-birth-weight premature infants. Four patients seen early in this series required revision of the position of the pleural catheter, with successful drainage in each instance. Pleuroperitoneal shunting is a safe, simple, and effective treatment of chylothorax in infants and children. In view of our success in treating chylothorax with these shunts, we recommend early shunting before the development of nutritional or immunological depletion.

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Successful management of chylothorax has always presented a difficult clinical challenge. Regardless of the cause, the presence of chylothorax produces respiratory compromise secondary to compression of the lung from the pleural effusion, and nutritional and immunological depletion secondary to the loss of fats, protein, and lymphocytes. Patients are initially treated with restriction of dietary fats using total parenteral nutrition or oral medium-chain triglycerides. Drainage of the pleural fluid is accomplished either by thoracentesis or tube thoracostomy. If these methods fail, surgical therapy is undertaken.

The goal of surgical therapy is twofold: first, to relieve the respiratory embarrassment by draining the pleural space, allowing reexpansion of the lung, and second, to stop the loss of the nutritional elements and immunological cells present in the chyle. Traditionally, there have been a number of surgical options available for the treatment of refractory chylothorax, including chemical pleurodesis, pleurectomy, and thoracotomy with thoracic duct ligation.

In 1983, our group [1] presented the use of pleuroperitoneal shunts in a group of 5 infants with chylothorax secondary to superior vena cava thrombosis. We have now used this technique in 16 children. A review of this clinical experience forms the basis for this report.

Material and Methods

Patient Population

Between June 1981 and June 1988, 16 patients with refractory chylothorax were seen on the Pediatric Surgical Service at the University of Virginia Health Sciences Center. They ranged in age from two days to 16 years. The cause of the chylothorax was congenital in 3 and acquired in the others (Table 1).

All 16 patients were initially treated with dietary manipulations, either restriction of oral fat intake to medium-chain triglyceride oil or placement on total parenteral nutrition. The pleural space was drained by thoracentesis or tube thoracostomy in each patient. When these methods failed to relieve the flow of chyle from the chest tube or reaccumulation of chyle within the chest, a pleuroperitoneal shunt was placed.

Technique

Early in this series, a Hakam/Cordis low-pressure ventriculoperitoneal shunt catheter system (Cordis Corporation, Miami, FL) was used. In 1983, we began to employ a specially designed Denver pleuroperitoneal shunt system (Codman & Shurtleff, Inc, Randolph, MA), which has functioned more effectively. This shunt has a flexible, double-valved pumping chamber and appropriately fenestrated afferent and efferent catheters that can be trimmed to the proper length. The shunt is manufactured with two sizes of pumping chambers. The pediatric chamber has a pumping volume of 1.0 to 1.5 mL and is used for infants less than 4 to 6 months of age. The adult chamber pumps 1.5 to 2.0 mL and is used for older patients. The valves open at a positive pressure of approximately 1 cm H_2O, and are designed to prevent retrograde movement of the chyle through the system. Manual pumping is used

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Table 1. Summary of Patient Data

Patient No.	Age	Etiology	Treatment	Shunt	Complication	Result
Idiopathic						
1	3 mo	Idiopathic	Drainage, 3 mo	Left	Pleural revision	Cleared
2	2 wk	Hydrops	Drainage, 15 days	Right	None	Cleared
3	6 wk	Idiopathic	15 days	Right	None	Cleared
Acquired: Thoracic Procedure						
1	8 mo	TGA, Senning	Drainage, 1 mo	Right	Pleural revision	Cleared
2	2 days	Pulmonary atresia, Waterston-Cooley	Drainage, 8 days	Right	None	Cleared; died of cardiac-related cause
3	18 mo	TGA, Senning	Drainage, 5 wk	Bilateral	Pleural revision	Cleared
4	10 mo	Atrioventricular canal	Drainage, 15 days	Right	None	Cleared
5	12 mo	TGA, Senning	Drainage, 7 days	Bilateral	None	Cleared
6	8 mo	TGA, Senning	Drainage, 8 days	Right	None	Cleared
Acquired: Caval Thrombosis						
1	2 mo	PDA ligation, central venous catheterization	Drainage, 5 wk	Bilateral	Exteriorization	Failure; died
2	3 mo	PDA ligation, central venous catheterization	Drainage, 5 wk	Left	None	Failure; died
3	3 wk	PDA ligation, central venous catheterization	Drainage, 4 wk	Bilateral	Ascites	Failure; died
4	6 wk	PDA ligation	Drainage, 9 days	Left	None	Cleared
5	8 mo	Neuroblastoma, central venous catheterization	Drainage, 14 days	Bilateral	Exteriorization, ascites	Failure
Acquired: Lymphangiomas						
1	16 yr	Lymphangioma	Bilateral pleurectomy; thoracic duct ligation	Pericardial, left pleural	None	Cleared
2	1 mo	Lymphangioma	Drainage, 1 mo	Pericardial, right pleural	Exteriorization	Cleared

PDA = patent ductus arteriosus; TGA = transposition of the great arteries.

to transport fluid from the pleural space into the peritoneal cavity, as pleural pressure rarely, if ever, exceeds peritoneal pressure under physiological conditions.

The technique for insertion of the shunt in children involves the use of general anesthesia. The affected hemithorax is elevated 30 degrees on the operating table (Fig 1A). The patient's chest and abdomen are widely prepared and draped. The shunt is soaked for 15 to 30 minutes in bacitracin solution as the operative procedure proceeds. The pumping chamber must be placed along the costal margin to provide a firm base for subsequent compression (Fig 1B). It is useful to place the shunt over the patient's chest prior to making any skin incisions to plan the route of the afferent and efferent catheters.

A short transverse incision is made over the lower chest in the anterior axillary line (Fig 1C). This incision affords access for the pleural catheter, which is tunneled 2 to 3 cm through the subcutaneous tissues. The catheter is placed bluntly into the thorax by passing it over the surface of a rib and through the intercostal muscles in the middle to posterior axillary line (Fig 2A, B). Proper positioning of this catheter is critical; it must not be allowed to kink as it passes across the chest wall. Through this same incision, a subcutaneous pocket is developed inferiorly for placement of the pumping chamber.

A second small incision is made over the midrectus sheath in the upper abdomen. A tunneling device is passed from the abdominal incision to the thoracic incision, and is kept directly on the muscle fascia to allow a thick subcutaneous covering of the pumping chamber and catheter (Fig 2C). The efferent catheter is drawn into the abdominal incision, and with traction on this catheter, the

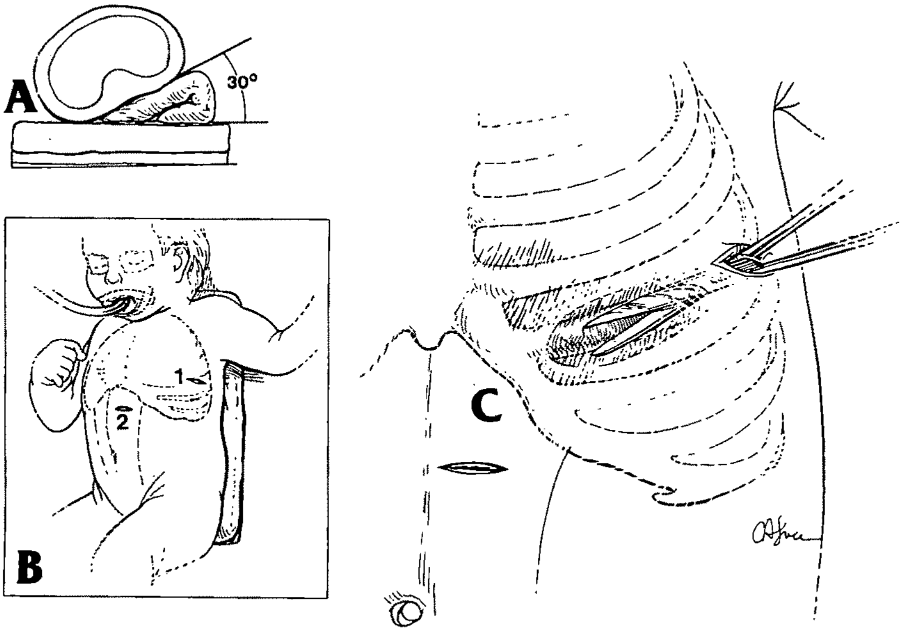

Fig 1. Insertion of pleuroperitoneal shunt. (A) The affected hemithorax is elevated 30 degrees. (B) The two incisions are planned to allow the chamber to rest on the costal margin. (C) A small incision is made over the rib in the anterior axillary line, and a deep subcutaneous pocket is created inferiorly.

pumping chamber is drawn into the subcutaneous pocket (Fig 3A). Two sutures can be used to secure the base of the pumping chamber to the thoracic fascia, although these have not been employed in all cases.

The anterior rectus sheath is divided transversely, and the fibers of the rectus abdominis muscle are split to expose the posterior rectus fascia (Fig 3B). A pursestring suture of 5-0 Prolene is placed in the posterior fascia, and the fascia and peritoneum are opened. Prior to placement of the peritoneal catheter, the pumping chamber is repeatedly compressed to confirm effective pumping action and proper transport of chyle (see Fig 3A). The efferent catheter is then placed into the peritoneal cavity after it has been trimmed to approximately 25 cm of catheter length in the abdomen (Fig 3C). The anterior rectus sheath is closed with nonabsorbable suture material, and the rest of the incisions are closed with absorbable subcutaneous and subcuticular sutures (Fig 3D). A postoperative chest roentgenogram should be obtained to confirm proper placement of the pleural catheter (Fig 4).

Immediately after placement of the shunt, the pumping chamber must be compressed from 50 to 100 times an hour to completely clear the hemithorax of chyle. This frequency of pumping is necessary because of the relatively small volume delivered with each compression. It is important that shunt compression be performed slowly so as to allow sufficient time for the pumping chamber to fill. The effectiveness of the pleural drainage can be determined by plain chest roentgenography or thoracic ultrasonography. Measurement of the abdominal girth should

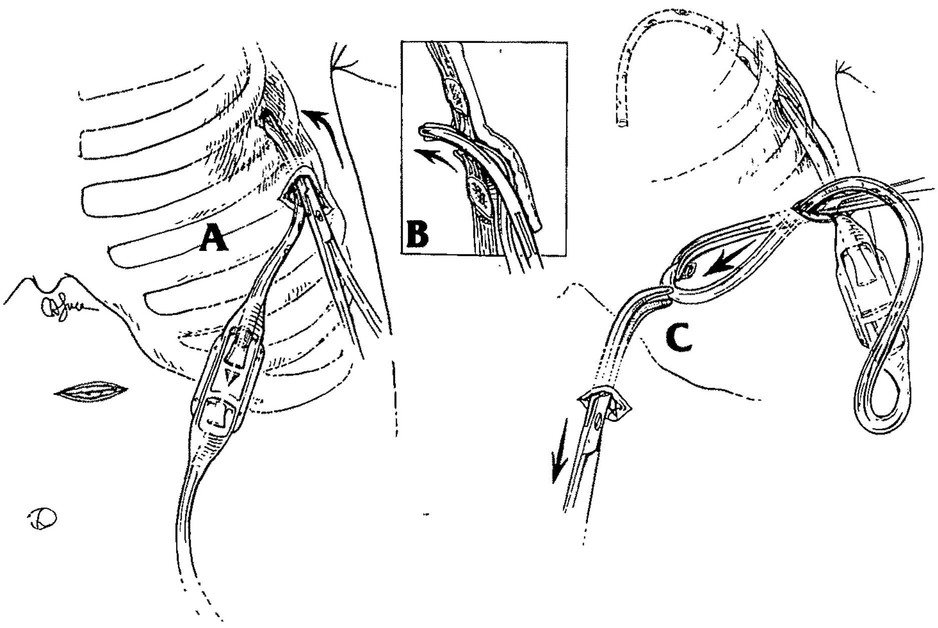

Fig 2. Insertion of pleuroperitoneal shunt. (A) The pleural catheter is tunneled 2 to 3 cm and bluntly passed through the intercostal musculature. (B) The catheter must be carefully passed through the musculature at an angle to avoid kinks. (C) A second small incision is made overlying the rectus muscle, and the peritoneal catheter is tunneled to this incision.

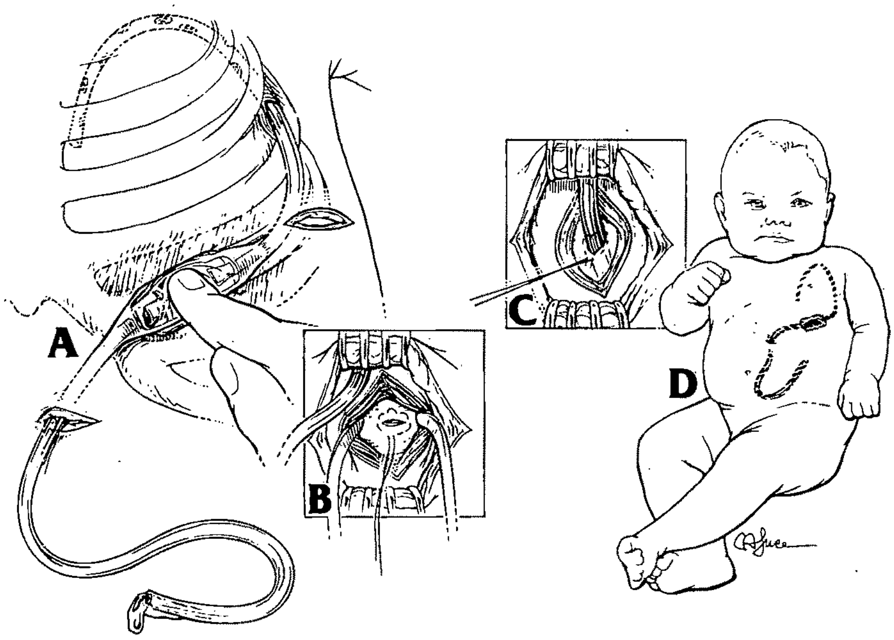

Fig 3. Insertion of pleuroperitoneal shunt. (A) The pumping chamber is drawn into the subcutaneous pocket by traction on the peritoneal catheter. It is important that the chamber be placed over a rib for a firm base for pumping. The chamber can be fixed into this position by suturing the base to the thoracic fascia. Flow through the shunt is confirmed before the peritoneal catheter is inserted. (B) The anterior rectus sheath is opened, and the rectus abdominis muscle fibers are divided. A pursestring suture is placed in the posterior rectus fascia. (C) The peritoneal catheter is placed in the abdominal cavity, and the pursestring suture is secured. (D) Both incisions are closed with absorbable sutures, leaving a totally implanted system.

be recorded for several days after operation to assess the amount of fluid transferred to the peritoneal cavity.

Once the chylous effusion clears, the pumping frequency is gradually decreased and the parents are taught the technique. The patients are usually discharged from the hospital on a regimen that includes compression of the chamber for approximately 60 times four times daily for the first month after discharge. Over the ensuing 2 to 3 months, the frequency of pumping is further reduced, and the catheter system can be removed if the effusion does not recur after 1 month of compression of the chamber.

Results

In 6 of our patients, chylothorax occurred after a cardiac procedure. Four of the 6 had a Senning atrial inversion procedure for transposition of the great arteries. In a neonate, a Waterston-Cooley shunt was created for pulmonary atresia, and another infant underwent correction of an atrioventricular canal. The cause of the chylothorax in these 6 patients was presumed to be secondary either to mediastinal dissection or to superior vena cava hypertension due to partial baffle obstruction. Baffle obstruction was documented in 2 patients by echocardiography. The age of these patients ranged from two days to 18 months. The average number of days of chest drainage before placement of the shunt was 17.

All 6 patients responded completely to pleuroperitoneal shunting. Each had rapid clearing of the pleural effusions and improvement in respiratory function. Two of these infants required bilateral shunt placement for bilateral effusions. There was a single death in this group, the two-day-old infant requiring palliation for pulmonary atresia. A right-sided shunt resolved the chylothorax, but the infant died at home several months later of cardiac failure. All of the remaining shunts have been removed without any recurrence of the chylothorax. Patients in whom chylothorax develops after thoracic surgical procedures appear to respond particularly well to early pleuroperitoneal shunting.

The 5 patients with chylothorax developing secondary to superior vena cava thrombosis after central venous catheterization did poorly compared with the 6 in whom chylothorax occurred after operation. The patients in this group tended to be small, 4 of the 5 weighing less than 1,500 g. Their age ranged from 3 weeks to 8 months. Four (80%) of the 5 patients in this group failed to respond to pleuroperitoneal shunting, and 3 of the 4 died of nutritional failure. Three of the 4 were premature infants operated on early in this series, and each presented technical difficulties related to their small size. In 3 of them, clinical evidence of inferior vena cava hypertension was present, either secondary to congestive cardiac failure or concomitant inferior vena cava thrombosis.

One child with metastatic neuroblastoma had thrombosis of both the superior and inferior venae cavae from multiple intravenous access procedures for chemotherapy. Such severe chylous ascites developed after placement of bilateral pleuroperitoneal shunts that the patient required paracenteses to allow effective ventilation. We considered placing a subsequent peritoneovenous shunt in this patient, but could not locate an adequate vein for drainage. He ultimately responded to shunt removal and bilateral talc poudrage. It appears that inferior vena cava thrombosis or hypertension can constitute a contraindication to placement of a pleuroperitoneal shunt, as the increased hydrostatic pressure in the inferior vena cava appears to impede the absorption of the chyle, resulting in the development of chylous ascites.

All 3 of the patients with idiopathic chylothorax did well after pleuroperitoneal shunts were placed. These infants ranged from 2 weeks to 3 months in age, and had drained chyle for an average of 40 days prior to shunting. The shunt has been removed in each without any recurrence of the chylothorax.

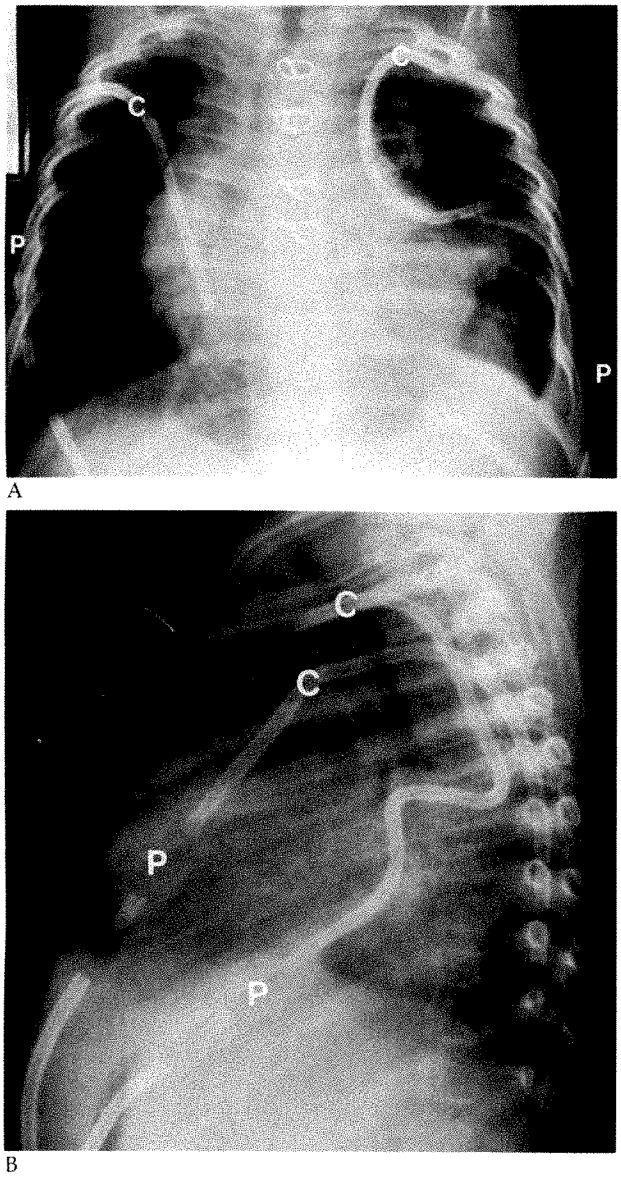

Fig 4. (A) Anteroposterior and (B) lateral chest roentgenograms demonstrating the position of the pleural catheters (C) and the pumping chambers (P). Bilateral chylothoraces have been completely evacuated.

Both of the patients with a mediastinal lymphangioma responded to the placement of a pleuroperitoneal shunt. The first was a 16-year-old boy with pericardial and pleural chylous effusions secondary to an extensive lymphangioma. This patient had previously undergone bilateral thoracotomies with ligation of multiple lymphatic leaks and pleurectomies. A persistent left chylothorax and chylopericardium was treated with a pleuroperitoneal shunt with the afferent catheter placed across the left pleural space into the pericardial space. This patient continues to use the shunt 2 years after its insertion to alleviate dyspnea during vigorous exercise.

The second patient with a mediastinal lymphangioma was seen at birth with pericardial and pleural effusions. She underwent placement of a shunt from the pericardial space to the peritoneum, but marked bradycardia developed with compression of the pumping chamber. The chamber was subsequently exteriorized, and a second exteriorized system was placed in the right pleural space with rapid and complete clearance of the effusions. She was discharged, and the parents compressed the shunt on a regular basis. The entire system was removed 8 weeks later without recurrence of the effusions.

Comment

Chylothorax is an uncommon condition resulting from accumulation of lymph in one or both hemithoraces. Chylothorax can be classified as either congenital (idiopathic) or acquired. Acquired chylothorax can be secondary to mediastinal malignancies (commonly lymphoma), trauma, thoracic operations, caval thrombosis, or mediastinal lymphangiomas. Chyle does not cause pleural inflammation, and symptoms usually relate to pulmonary compression [2]. Chyle is considered to be bacteriostatic, and infections in these effusions are rare.

The diagnosis of chylothorax can be confusing in the absence of normal oral intake, as was the case with most of our patients. The characteristic "milky" appearance of the fluid is lost as the fat content of the fluid decreases. Chemical analysis of normal chyle reveals a protein content of between 2.2 and 5.9 g/dL. The triglyceride content ranges between 0.4 and 4 g/dL, depending on the dietary intake of fat. The most helpful laboratory test for diagnosing chylothorax in our experience is the Gram stain and cell count. Chyle, even in the fasting patient, contains a marked preponderance of lymphocytes (80%) with cell counts ranging between 400 and 6,000/mL.

Unlike serous pleural effusions, which may respond to diuretic therapy or alterations in plasma oncotic pressure, the treatment of chylous pleural effusions requires more aggressive measures. The initial therapy for these effusions should involve complete drainage of the pleural space with thoracentesis or tube thoracostomy. Attempts to diminish thoracic lymphatic flow with total parenteral nutrition and enteral feedings with medium-chain triglycerides are also employed [3, 4]. The medium-chain triglyceride molecules are absorbed directly into the portal venous system, bypassing the intestinal lymphatics completely.

Although opinions vary, most authors recommend an extended period of conservative management before instituting operative measures, even though this is often accompanied by severe nutritional and immunological disturbances. Selle and colleagues [5] have suggested that surgical intervention is indicated when the daily loss of chyle exceeds 1,500 mL in adults or 100 mL per year of age in children for a five-day period, when chyle flow has not diminished over a period of 14 days, or when nutritional complications appear imminent. It is unclear from the small series of patients with chylothorax reported in the literature how often nonoperative management is successful, although in the experience of our group [6], only 1 patient of 20 survived without an operation.

If conservative therapy fails to resolve the chylothorax, several surgical options exist. The technique that has been advocated by most is transthoracic ligation of the thoracic duct, described by Lampson [7] in 1948. This technique has been reported to be successful in as many as 90% of patients but requires an extensive thoracotomy [8, 9]. Other techniques suggested in isolated case reports include chemical pleurodesis with tetracycline hydrochloride or talc and pleurectomy [10, 11]. Both of these procedures attempt to create a pleural symphysis and develop collateral lymphatic pathways.

In 1983, our group [1] reported the use of pleuroperitoneal shunts in the treatment of refractory chylothorax in 5 ventilator-dependent premature newborns. Pollock [12] had previously described using a pleurovenous shunt in the treatment of a patient with a malignant pleural effusion. The potential for the development of a pneumothorax, with subsequent air embolus, however, made this technique less attractive. Weese and Schouten [13] reported in 1982 the use of a pleuroperitoneal shunt in 2 adults with malignant pleural effusions; the results were excellent.

Our experience with this technique in 16 infants and children with chylothorax has convinced us to adopt an aggressive surgical approach to this problem. Our experience indicates the importance of careful patient selection for the use of these shunts. If one eliminates the 3 infants with inferior vena cava hypertension from the analysis, pleuroperitoneal shunts successfully relieved the chylothorax of 12 (92%) of 13 patients. Chylothorax as a consequence of caval thrombosis was reported by Vain and colleagues [14] in 1980, and the particularly lethal nature of this complication has been noted subsequently by several authors [15–17]. Alternative forms of therapy must be devised for infants in this category in whom pleuroperitoneal shunting fails.

In this review, specific technical aspects of the insertion of the pleuroperitoneal shunts and the postoperative management have emerged as critically important. Four (25%) of the patients required repositioning of the pleural catheter to achieve adequate transport of chyle. In each instance, the pleural catheter had kinked as it passed through the chest wall. Careful positioning of this end of the shunt system and creation of a gently angled tunnel through the intercostal musculature are important. We have performed this bluntly, although Little and associates [18] have advocated using the Seldinger technique. Frequent, slow compression of the pumping chamber must be performed immediately after operation because of the small volumes of the chambers. This has created some problems with chest wall pain and interruption of the sleep cycle in our smaller patients. Intractable difficulties necessitated exteriorization of the pumping chamber in 3 patients, and 1 infant was successfully managed at home with exteriorized chambers. We have not encountered reluctance or inability of the parents of our patients to pump the chambers on a regular schedule, but Little and co-workers [18] had 3 adults who were unable or unwilling to compress their own chambers.

Pleuroperitoneal shunting is a safe and simple method for treatment of refractory chylothorax. The insertion of these shunts is so much less involved and better tolerated than the conventional practice of thoracic duct ligation that earlier intervention is justified. The shunts have proved to be at least as effective as other surgical methods, and provide for retention of the nutritional and immunological elements of the chyle. In view of our success with these shunts and similar success reported by others [18–20] in treating malignant effusions, we recommend placement of a pleuroperitoneal shunt in any patient with documented chylothorax and persistent drainage for more than five days.

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Esophageal Carcinoma: Surgery Without Preoperative Adjuvant Chemotherapy

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Our experience with 100 consecutive patients with esophageal carcinoma treated with surgical intervention as the primary method of therapy between 1967 and 1987 was reviewed. Preoperative chemotherapy was not administered by us. Follow-up was complete for all 100 patients. Twelve percent of tumors were in the proximal third of the esophagus, 21% were in the middle third, and 67% were in the distal third. Adenocarcinoma accounted for 44% of all tumors, squamous cell for 55%, and adenosquamous for 1%. Six patients were in stage I, 14 were in stage II, and 80 were in stage III; no patient was in stage IV. Surgical procedures included 85 esophagogastrectomies with primary anastomoses, 11 with colon interposition, and 4 with Roux-en-Y small-bowel interposition. Six patients had radical laryngopharyngoesophagectomy with gastric or colopharyngeal anastomosis. Operative mortality was 3%. The mean survival of stage I patients was 182 months; stage II patients, 25 months; and stage III patients, 18 months. Our data show that surgical resection without preoperative adjuvant chemotherapy remains the cornerstone of therapy for patients with carcinoma of the esophagus.

(Ann Thorac Surg 1989;48:201–5)

Controversy continues over the most effective means to treat carcinoma of the esophagus. Despite recent advances in adjuvant therapy, little or no improvement in long-term survival has been reported. Surgical therapy continues to be the cornerstone of nearly all treatment protocols, and is the only consistently effective modality for achieving substantial palliation and survival for these patients.

The overall benefit of newer protocols using adjuvant therapy remains uncertain. However, operative mortality rates of as high as 20% to 30% [1] have prompted some authors to advocate resection only if cure can be obtained. Reports [2–5] of preoperative adjuvant therapy producing improved resectability, decreased host tumor burden, and improved 2-year survival have been published, but they describe relatively few patients and show only a small or no improvement in outcome.

Our philosophy is to offer curative resection to patients with carcinoma of the esophagus at all levels—cervical, midthoracic, and distal—who have no obvious metastatic disease [6]. We do not advocate preoperative chemotherapy or radiotherapy; rather we consider them only for unresectable lesions or for postoperative application in patients with nodal disease. Our goal is to rapidly restore the patient's ability to swallow and improve his or her quality of life while attempting to prolong survival as far as possible.

In view of recent reports describing improved resectability and survival with adjuvant chemotherapy or radiation therapy, we elected to review our experience at Emory University Hospital with 100 consecutive patients treated with surgical intervention as the primary therapeutic modality. We intended to determine if our results with aggressive surgical therapy alone were surpassed by the results obtained employing newer adjuvant techniques. Our population was analyzed by both tumor stage and histology to determine factors contributory to survival.

Material and Methods

The records of 100 patients with esophageal carcinoma treated at Emory University Hospital by one of us (K.A.M.) from 1967 to 1987 were retrospectively reviewed. Follow-up was complete for all 100 patients, and all were followed for up to 18 years or until death.

All patients were preoperatively staged by clinical, radiographic, and endoscopic means. Curative or palliative operative intervention was offered to all with preoperative stage I, II, or III disease as defined by the American Joint Commission on Cancer [7].

Surgical procedures included 85 esophagogastrectomies with primary esophagogastric anastomoses, 11 esophagogastrectomies with colon interposition, and 4 esophagogastrectomies with Roux-en-Y small-bowel interposition in patients with a previous gastrectomy. Six patients underwent radical laryngopharyngoesophagectomy with gastric or colopharyngeal anastomosis.

Our technique of transthoracic esophagogastrectomy using a midline abdominal incision and right thoracotomy incision was the same throughout the series. The esophagus was divided some 10 cm proximal to the palpable margin of the tumor. When extramural extension was encountered, en bloc resection of the tumor with the adjacent nodes was performed. All esophageal anastomoses were made using a double layer of interrupted 3-0 silk.

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Table 1. Patient and Tumor Characteristics

			Location in Esophagus			Type of Carcinoma	
Stage	No. of Patients	Male : Female	Proximal	Middle	Distal	Adenocarcinoma	Squamous Cell
I	6	3 : 3	1	2	3	1	5
II	14	10 : 4	0	3	11	5	9
III	80	62 : 18	11	16	53	38	41
Total	100	75 : 25	12	21	67	44	55[a]

[a] One patient had adenosquamous cancer.

A pyloroplasty was performed in all patients with esophagogastric anastomosis.

Parenteral hyperalimentation was begun immediately postoperatively if it had not been initiated before operation. A routine esophagogram was obtained by the seventh postoperative day, and if no leak was demonstrated, oral feedings were started. All patients who were discharged from the hospital tolerated a regular diet well.

Adjuvant therapy was administered, often outside the protocol, by the referring physicians. Fourteen patients received preoperative external-beam radiation therapy (stage I, 1 patient; stage II, 3 patients; stage III, 10 patients) consisting of 2,000 rads, and 2 patients received preoperative chemotherapy with no response. Postoperative adjuvant therapy was offered to all patients with residual disease or positive mediastinal or celiac lymph nodes. Thirty-four patients (stage I, 5; stage II, 7; stage III, 22) received postoperative radiation therapy, 2,000 to 5,000 rads. Twelve patients (stage I, 2; stage III, 10) received postoperative chemotherapy including 5-fluorouracil, methotrexate, *cis*-platinum, mitomycin-C, or Adriamycin (doxorubicin hydrochloride). Four stage III patients received both radiation therapy and chemotherapy after operation. The remaining patients received no adjuvant therapy.

The Kaplan-Meier survival curves and median survival times for each group were determined using the EMOPIL Life Tables and Survival Functions software package (EMOP Statistical Software, Inc, Los Angeles, CA). Statistical significance was determined by the generalized Wilcoxon (Breslow) [8] and Savage (Mantel-Cox) [9] tests.

Results

One hundred complete charts were available for review. A 3:1 male to female predominance was found. The mean age was 61 years (age range, 31 to 84 years). Patient and tumor characteristics are shown in Table 1. Twelve percent of all tumors were located in the proximal third of the esophagus, 21% in the middle third, and the remainder in the distal third. Adenocarcinoma accounted for 44% of all tumors, the majority being found in the distal third of the esophagus. Squamous cell carcinoma accounted for nearly all stage I tumors, while adenocarcinoma and squamous cell carcinoma occurred with nearly equal frequency in stage III patients. Six patients had only mucosal disease; two of the lesions were in situ lesions.

The actuarial 5-year survival of all patients is shown in Figure 1. The mean actuarial survival of all stage I patients was 182 months, which is significantly greater than the survival of those with either stage II (25 months) or stage III disease (18 months) (Table 2). Survival of stage I patients was markedly skewed by the long-term survival (216 months) of 1 patient. Nonetheless, survival of all patients in this group was significantly better than that of stage II or III patients. Although we found a numerically better actuarial survival for stage II compared with stage III patients, the difference was not significant, and furthermore, median survival for each stage was quite similar (stage II, 8 months; stage III, 8 months).

Survival was analyzed by histological group (see Table 2). Combined actuarial survival for patients with stages I, II, and III squamous cell carcinoma (29.5 months) was not significantly different from survival for all patients with adenocarcinoma (28 months).

Survival was next analyzed with reference to type of treatment (see Table 2). Evaluation of patients in stages II and III with adenocarcinoma treated by surgical intervention plus adjuvant therapy showed a survival approximately two times that of patients with adenocarcinoma treated with operation alone. However, this difference was not significant by either the Wilcoxon or Savage method of analysis. Furthermore, the median survival for each of these groups was nearly identical (10 months versus 13 months), which indicates the data for the adenocarcinoma group given adjuvant therapy was

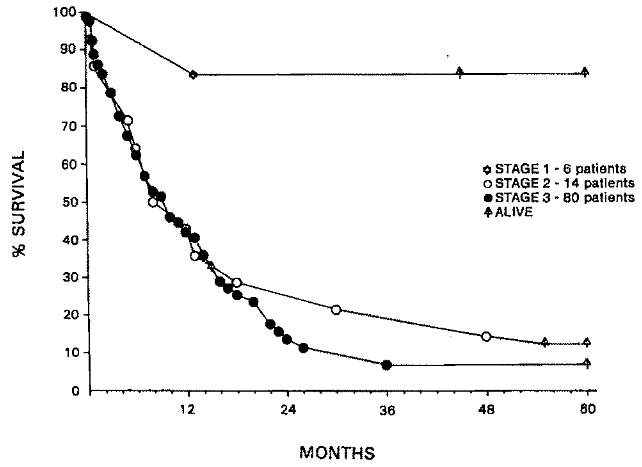

Fig 1. Actuarial 5-year survival for all 100 consecutive patients having resection of esophageal carcinoma from 1967 to 1987.

Table 2. Survival Characteristics

Variable	No. of Patients	Survival[a] (mo)	Median Survival (mo)	*p* Value (Wilcoxon, Savage)
Stage				0.067, 0.002
I	6	182.2 ± 43.7	68	
II	14	25.0 ± 8.9	8	
III	80	17.7 ± 3.7	8	
Tumor histology (all stages)				0.100, 0.140
Squamous cell	55	29.5 ± 9.8	8	
Adenocarcinoma	44	28.0 ± 6.4	13	
Adenosquamous	1	. . .		
Treatment (stages II and III combined)				
Adenocarcinoma				0.900, 0.430
Surgery	18	17.1 ± 2.9	13	
Surgery + postop adjuvant treatment	25	35.8 ± 10.9	10	
Squamous cell carcinoma				0.020, 0.140
Surgery	25	12.5 ± 2.4	7	
Surgery + postop adjuvant treatment	25	15.3 ± 6.2	4	
Contribution of postop adjuvant therapy (stages II and III combined, adenocarcinoma and squamous cell combined)				0.110, 0.900
Surgery	43	14.5 ± 1.9	8	
Surgery + postop adjuvant treatment	50	24.4 ± 6.1	6	

[a] Data are shown as the mean ± the standard error of the mean.

skewed by a single survivor at 132 months. A nearly equal survival was found for patients with squamous cell carcinoma treated by operation plus adjuvant therapy compared with patients treated by surgical intervention alone (15.3 months versus 12.5 months). The median survival for each group was similar and was poor in each instance. Therefore, survival of patients with either tumor histology was essentially unchanged by the adjuvant treatment.

To evaluate the overall contribution of adjuvant therapy to survival without regard for histology, combined stage II and III patients who underwent surgical resection alone were compared with those treated with both surgical intervention and adjuvant therapy (see Table 2). Despite an approximately 60% numerical survival advantage for patients who received adjuvant therapy, the difference was not significant by either method of analysis. Furthermore, the median survival of each group was nearly the same (8 months versus 6 months). Survival of the adjuvant treatment group was skewed by the data for 2 patients, 1 who survived for 82 months and 1 who survived for 98 months.

Complications not directly caused by the tumor per se are shown in Table 3. Some patients experienced more

Table 3. Complications

Complication	Early (30 days)	Late
Major		
Death	3	5
Anastomotic leak	6	0
Colon segment necrosis	1	0
Anastomotic stricture	0	9
Adult respiratory distress syndrome	8	0
Pulmonary embolus	1	0
Pneumonia	2	0
Myocardial infarction	1	0
Acute renal failure	3	0
Minor		
Gastroesophageal reflux	0	5
Small-bowel obstruction	0	3
Enterocutaneous fistula	0	1
Costochondritis	1	0
Syndrome of inappropriate secretion of antidiuretic hormone	1	0

than one complication. The 30-day mortality was 3% (3 patients). Two patients died of sepsis from anastomotic leakage, and 1 patient died intraoperatively of a myocardial infarction. There were 5 late deaths, all of which were unrelated to tumor; 1 death due to suicide, 1 death due to hepatitis at 13 months, and 3 deaths due to atherosclerotic disease (two myocardial infarctions, one at 3 and one at 6 months, and one cerebrovascular accident at 2 months). Anastomotic stricture was the most frequent late complication (9%), and was successfully managed in all instances by endoscopic dilations.

Comment

Despite the advent of protocols involving preoperative and postoperative chemotherapy and radiation therapy, survival of patients with esophageal cancer remains poor. Although adjuvant modalities have been associated with modest response rates and improved tumor resectability [2, 3, 10, 11], prolonged survival has not yet materialized. Surgical resection remains the cornerstone of immediate palliation, and provides the definitive means of treatment and the best opportunity for cure.

Review of our series of consecutive surgical patients confirms the well-described differentiation in patient survival related to tumor stage. For patients with stage I disease, prolonged survival and even cure can be achieved, eg, 2 of our patients with in situ carcinoma were cured by surgical treatment alone. Similarly, excellent long-term survival was achieved with surgical treatment alone in the remaining stage I patients, and none of these patients have subsequently had recurrent disease.

In contrast, spread of disease beyond the mucosa into the esophageal wall (stage II) or beyond (stage III) is associated with a marked reduction in patient survival. The dismal effect on survival when there is tumor penetration beyond the mucosa suggests a systemic disease that is not curable by aggressive local resection.

Because the overwhelming majority of deaths result from systemic disease, the only foreseeable hope for prolonged survival of advanced-stage patients appears to be the development of an adjuvant therapy that can successfully eradicate the systemic tumor. Recent enthusiasm for combination preoperative chemotherapeutic protocols is encouraging, but to date, the results are inconclusive. Using such methods, some authors [10, 12] have described a reduction in tumor bulk or complete disappearance of tumor on postoperative histological examination, and resectability is therefore said to be improved. However, an improvement in systemic disease status has not yet materialized, and neither has long-term survival been noticeably improved. In addition, because of the recent development of these protocols, long-term (5 to 10 years) follow-up remains unavailable.

The other drawbacks of preoperative chemotherapy have been incompletely addressed. Factors that must be considered include substantial prolongation of hospitalization, delay in relief of obstructive symptoms, the toxic side effects of these agents, secondary delay in recovery from operation, and the increased financial cost of these protocols, particularly in view of the continuing dismal survival data.

Therefore, aggressive surgical resection continues to be the cornerstone of treatment for esophageal carcinoma. Our data show patients can be offered nearly immediate palliation of tumor-induced obstructive symptoms with minimal short-term and long-term morbidity plus a 2-year and 5-year survival that is not improved with the use of adjuvant preoperative therapies. Although we believe prolonged survival in advanced-stage patients will be attained only by effective systemic treatments, such treatments have not yet materialized. Proposed preoperative adjuvant therapies will remain investigational until prospective randomized clinical trials confirm that multimodality therapy is superior to surgical resection alone.

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INVITED COMMENTARY

This report includes 6 patients with cancers that involved only the mucosa; they account for the outstanding results from resection of stage I disease. Operation without adjuvant therapy is certainly the current treatment of choice for such patients. Patients wih stage II and III cancers comprised 94% of the series, and about 60% of these patients died within 1 year of resection. Therefore, the success of treatment should be judged on the basis of the speed and ease with which it becomes effective.

Before preoperative or postoperative adjuvant or alternative therapy can be considered standard, it must relieve dysphagia as promptly as resection, and it must improve the long-term cure rate. Based on these criteria, adjuvant therapy does not yet qualify either to delay resection or to add notable morbidity (or inconvenience) during the usually brief period of palliation. Adjuvant treatment should be employed primarily in the context of well-controlled studies designed to compare results with their use against the direct approach of proceeding promptly with resection as the treatment of choice.

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Notice From the Southern Thoracic Surgical Association

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Phoenician Golf and Tennis Resort, Scottsdale, AZ, November 9–11, 1989. There will be a $155 registration fee for the Scientific Session for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 9, 1989. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Advance registration forms, hotel reservation cards, and details regarding transportation arrangements will be mailed to Association members. Nonmembers should write to the Secretary-Treasurer, Gordon F. Murray, MD.

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Extracorporeal Membrane Oxygenation for Circulatory Support After Repair of Congenital Heart Defects

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Extracorporeal membrane oxygenation was used for cardiovascular support in 13 infants and children with complex congenital heart disease and 1 premature neonate treated in preparation for pericardial patch tracheoplasty for long-segment tracheal stenosis. Nine patients were weaned from extracorporeal membrane oxygenation. There were five (36%) early deaths and four (29%) late deaths. Cannulation sites included right carotid/jugular vessels, femoral artery and vein, and right atrium and aorta. In 4 patients, the neck vessels were repaired at decannulation. Five survivors had normal growth and neurodevelopmental evaluations at follow-up. Extracorporeal membrane oxygenation can be successfully used as biventricular support in patients with intractable low cardiac output syndrome after repair of congenital heart disease. Best results are obtained in patients who have several hours of stability after operation before initiation of support. Hemorrhagic complications are reduced and long-term neurodevelopmental outcomes appear promising with right neck vessel cannulation and repair. No bleeding complications were observed in patients cannulated through the neck vessels.

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Ventricular assist devices and balloon counterpulsation have been successfully used in adult patients for treatment of cardiogenic shock after cardiac operations. Such devices have had only limited use in the pediatric population due to size and technical problems as well as device failures [1–4]. Although the total number of patients has been small, a few reports [5–12] have described pediatric patients who experienced life-threatening refractory cardiopulmonary failure after repair of congenital heart disease and who were treated with extracorporeal membrane oxygenation (ECMO) for biventricular support.

Since July 1985, we have treated more than 70 pediatric patients with ECMO. Fourteen of these patients were treated with extracorporeal oxygenation for cardiorespiratory support in the perioperative period. This article outlines our experience and includes follow-up of 6 survivors.

Material and Methods

Patient Population

Between July 1985 and November 1988, 14 patients were placed on ECMO for cardiopulmonary support in the perioperative period (Table 1). Eight were male and 6 were female; age ranged from two days to 7.4 years (mean age, 1.42 years). The patients had a variety of complex congenital cardiopulmonary defects. In 12 patients, the indications for initiation of ECMO support included progressive hypotension, increasing ventricular filling pressures, poor peripheral perfusion, decreased urinary output, and decreased mixed venous oxygen saturations despite maximal pharmacological support. Five patients experienced refractory junctional tachycardia as part of low cardiac output syndrome. An additional patient (patient 3), a 1.1-kg 30-week estimated gestational age premature neonate was placed on ECMO on day 17 of life in preparation for a pericardial patch tracheoplasty for congenital long-segment tracheal stenosis. This infant's condition was severely unstable, with hypotension, acidemia, hypoxemia, and hypercarbia (arterial carbon dioxide tension > 260 mm Hg), and he was placed on ECMO support for resuscitation. After confirmation of adequate neurological function, repair of the trachea was performed using ECMO for ventilatory support. Extracorporeal membrane oxygenation was continued for six days after surgical repair of the trachea. Patient 13 was placed on ECMO preoperatively for circulatory support of biventricular failure secondary to congenital mitral regurgitation.

The ECMO circuit described by Bartlett and colleagues [13, 14] and used in our institution for neonatal pulmonary support was used for all postoperative patients. A SciMed (0.8 m^2) membrane oxygenator and Omnitherm heat exchanger (SciMed Life Systems, Minneapolis, MN) were connected to a 4-inch (10.16 cm) Polystan Verticlude direct drive roller pump (Polystan A/S, Copenhagen, Denmark) by $\frac{1}{4}$-inch (6.35 mm) tubing. The pump was

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Table 1. Patient Characteristics

Patient No.	Age (yr)	Diagnosis	Time to ECMO (h)	Time on ECMO (h)	Cannulation	Weaned	Outcome
1	4.8	AV canal, tetralogy	72	144	Fem/Fem	+	Hospital death (18 days)
2	3.3	EFE, transplant	4	121	Ao/RA	+	Hospital death (2 days)
3	17 days	Tracheal stenosis, PDA	Preoperative	87	Car/Jug	+	Hospital death (10 mo)
4	7.4	Single ventricle, Pul Atr	1	46	Fem/Fem	−	Died
5	0.5	AV canal, DORV	8	117	Car/Jug	+	Survived
6	1.2	Single ventricle, Pul St	12	59	Car/Jug	+	Survived
7	8 days	Hypoplastic left heart syndrome	OR	6	Ao/RA	−	Died
8	0.4	AV canal, CoA, Pul HTN	8	108	Car/Jug	+	Survived
9	0.2	TGA, VSD	OR	31	Ao/RA	−	Died
10	13 days	Truncus arteriosus	7	58	Car/Jug	+	Survived
11	1.3	Tetralogy	25	47	Ao/RA	+	Survived
12	0.6	Tetralogy	OR	56	Ao/RA	−	Died
13	10 days	Congenital MR, Pul HTN	Preoperative	269	Car/Jug	−	Died
14	2 days	IAA-B	OR	142	Car/Jug	+	Hospital death (12 days)
Mean	1.42		11.4				

Ao = aorta; AV = atrioventricular; Car = internal carotid; CoA = coarctation of the aorta; DORV = double outlet right ventricle; EFE = endocardial fibroelastosis; Fem = femoral; IAA-B = interrupted aortic arch type B; Jug = internal jugular; MR = mitral regurgitation; OR = operating room; PDA = patent ductus arteriosus; Pul Atr = pulmonary atresia; Pul HTN = pulmonary hypertension; Pul St = pulmonary stenosis; RA = right atrium; TGA = transposition of the great arteries; VSD = ventricular septal defect.

servo-controlled by a silicone venous reservoir in contact with a switch that automatically inactivates the roller pump if reservoir volumes fall below a preset level. A recirculating water heater was connected to the heat exchanger and temperatures were maintained at 38°C. Initial flow rates were set at 100 to 120 mL/kg/min. The patients' blood gases were monitored and adjusted by altering the sweep rate and composition of the gases passing across the membrane. After heparin anticoagulation (1.5 mg/kg), the activated clotting times were monitored and heparin infusions were adjusted to maintain the activated clotting times at 200 to 220 seconds.

Three cannulation sites were used for the venoarterial bypass. In 5 patients a transthoracic approach was used. Cannulas were placed in the aorta and right atrium directly. In 3 of these patients who required ECMO support after they could not be weaned from cardiopulmonary bypass, the same bypass cannulas were left in place and connected to the ECMO circuit in the operating room. The cannulas were then brought through the sternotomy, and the sternum was loosely approximated. Femoral artery and vein cannulation was performed through a groin incision in 2 patients. The right common carotid artery and internal jugular vein were cannulated through a lateral neck dissection on the right in the remaining 7 patients; in 1 patient (patient 14) by extension of the median sternotomy incision. Four patients underwent vascular repair of the carotid artery and jugular vein at the time of decannulation.

After initiation of ECMO support, inotropic agents were rapidly decreased to low levels or discontinued and ventilatory rate and oxygen settings were reduced. Vasodilator therapy could often be instituted or increased after biventricular support with ECMO was started.

Echocardiographic and hemodynamic measurements were observed during brief periods of decrease in ECMO flow for evaluation of recovery of cardiac function. When the patient exhibited stable hemodynamics during trials of low flow, gradual weaning of flow rates to less than 100 to 200 mL/min with adjustment of ventilation and inotropic support was performed. Decannulation and vascular repair were performed in the intensive care unit for all patients except patient 14, who was stable and transported back to the operating room for decannulation of the neck vessels through median sternotomy incision and vascular repair.

Six patients were examined on follow-up 1 to 12 months after operation. Full neuromuscular examinations and the Denver Developmental Screening Tests were performed in 5. In 5 patients who had carotid-jugular cannulation, duplex Doppler examinations [15–17] of the neck vessels were performed with a range-gated pulse Doppler system (Acuson 128) with a 5-MHz linear phased-array transducer. Color-flow Doppler echocardiography was performed (Quad 1; Quantum Medical Systems) with a 7.5-MHz linear phased-array transducer. The circle of Willis was examined by color-flow Doppler echocardiography in patient 10 (neck vessels ligated) to evaluate the cerebral blood flow pattern.

Results

In our series, 12 patients had a time interval from operation to initiation of ECMO support of 0 to 36 hours (mean, 11.1 hours). Two patients were placed on ECMO before operation (Table 1). Peak flow rates were 0.8 to 2.4 L/min/m^2. The duration of ECMO support ranged from 6 to 269 hours (mean, 92.2 hours).

Nine of 14 (64%) patients were successfully weaned from ECMO. Five patients who could not be weaned from the device died (36%). Three patients who could not be weaned from cardiopulmonary bypass died in the operating room, 1 after a Norwood procedure for hypoplastic left heart, 1 after a Senning repair of transposition of the great vessels and closure of multiple ventricular septal defects, and 1 after reoperation for residual inlet-type ventricular septal defect and tetralogy of Fallot. Patient 4 was started on ECMO only one hour after completion of a central aortopulmonary shunt for palliation of univentricular heart with pulmonary atresia and severe cyanotic cardiomyopathy. She experienced intraoperative hypotension, bradycardia, and cardiac arrest. External chest massage was continued while the patient was placed on ECMO through the groin. Bleeding from the cannulation site, surgical lines, and endotracheal tube was excessive. The patient did not recover neurological function, and ECMO was discontinued. An additional patient was placed on ECMO for biventricular support for congenital mitral and tricuspid valve insufficiency and pulmonary hypertension in preparation for mitral valve replacement, which was successfully accomplished with carotid/jugular cannulas for perfusion during operation. Despite improvement in cardiac function, pulmonary hypertension did not resolve after valve replacement and the patient died shortly after being weaned from ECMO ten days later.

Four (29%) deaths occurred in the 9 patients successfully weaned from ECMO. The first patient experienced biventricular failure and progressive renal failure after repair of double-outlet right ventricle with pulmonary stenosis and inlet-type ventricular septal defect. He underwent dialysis while on ECMO; renal function returned while he was on ECMO therapy. Serious gastrointestinal bleeding and seizures complicated his course, and cannulation through the femoral vessels resulted in leg ischemia requiring fasciotomies. Although he was successfully weaned from ECMO and ventilatory support, an overwhelming fungal infection developed and he died 18 days later. Patient 2 died two days after ECMO decannulation after an acute elevation of pulmonary artery pressure with a resultant low output and hypoperfusion. Bleeding around the transthoracic cannulas also complicated her ECMO course. Patient 3 died 10 months after ECMO of bronchopulmonary dysplasia and chronic respiratory failure unrelated to ECMO. The fourth patient (patient 14) required support in the operating room after she could not be weaned from bypass after repair of interrupted aortic arch and ventricular septal defect. She died 12 days after ECMO decannulation secondary to repeated pulmonary hypertensive crises.

Table 2. Cannulation Follow-up

Patient No.	Site	Repair	Doppler
3	Neck	+	Not studied
5	Neck	+	Normal flow, 40% narrow
6	Neck	+	Normal
8	Neck	+	Normal flow, 40% narrow
10	Neck	–	Retrograde flow through left vessels
11	Transthoracic	–	Not studied
14	Neck	+	Normal

Of the 9 patients weaned from ECMO, 5 (36%) are late survivors. Two of these patients were placed on ECMO eight hours after atrioventricular canal defect repair (Table 1). Both had pulmonary hypertension preoperatively. Twelve hours after septation procedure and right ventricular outflow patch placement of univentricular heart and pulmonary stenosis, patient 6 required ECMO for low cardiac output syndrome. In patient 10, refractory supraventricular tachycardia and cardiac arrest developed seven hours after repair of truncus arteriosus type I. She was placed on the device while cardiopulmonary resuscitation was continued. Patient 11 had refractory right ventricular failure after repair of tetralogy of Fallot and required ECMO 25 hours after operation.

Six patients were evaluated 3 to 12 months after ECMO. Five had normal neurological and motor examinations. One had mild gross motor delay. Development was otherwise appropriate for age. None of the patients had residual seizure activity, and none were taking anticonvulsive medications at follow-up.

The cerebral vessels of 5 patients were examined using Doppler ultrasonography (Table 2). Patients 6 and 14 were normal. Patients 5 and 8 had slight narrowing of the carotid artery at the surgical site just below the carotid bulb. The carotid artery was 4 mm in diameter below the surgical site and 3 mm in diameter at the surgical site (Fig 1). No turbulent flow was noted in either patient. Patient 5 had a small piece of tissue protruding into the carotid vessel lumen at the anastomosis site. The internal jugular veins had normal flow; diameters could not be assessed. Patient 10 (right carotid/jugular ligated at decannulation) had normal left common, internal carotid, external carotid, and vertebral arteries. The left jugular vein was also patent. The right vertebral artery was well imaged; on the right there was no evidence of common carotid artery or internal jugular vein. Intracranial color Doppler imaging demonstrated normal flow in both anterior and middle cerebral arteries with reverse flow in the A-1 segment of the right middle cerebral artery and in the proximal portion of the internal carotid artery.

Complications were common in our patients (Table 3). The most frequent problems were tachyarrhythmias, which were noted before ECMO and contributed to the

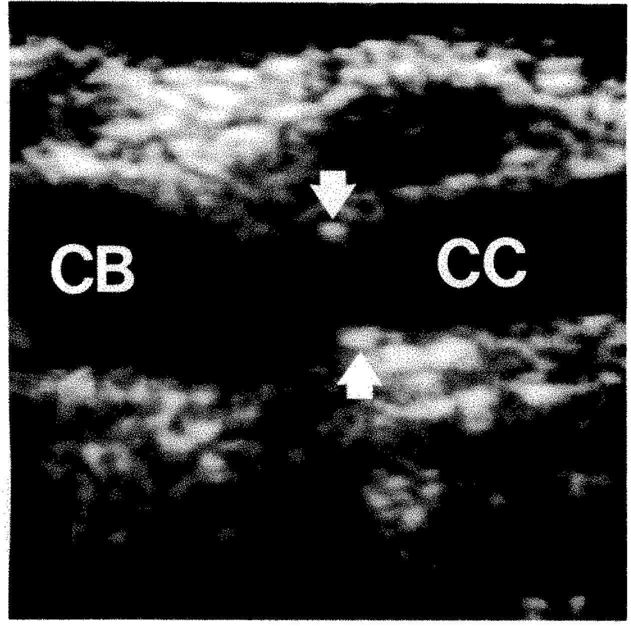

Fig 1. Two-dimensional ultrasonogram of the right carotid artery in longitudinal view. A narrowing is apparent (arrows) *at the surgical site in the common carotid artery* (CC) *below the carotid bulb* (CB).

indications for cannulation. Junctional tachycardia, associated with the low cardiac output syndrome, was noted in 5 (36%) patients and resolved soon after hemodynamic stabilization on ECMO and weaning of inotropic agents. Bradycardia, supraventricular tachycardia, and surgically induced heart block were each noted in 1 patient.

Infection occurred in 2 patients (14%). One patient (patient 1) died after *Escherichia coli* and *Candida* sepsis developed. Patient 5, a late survivor, was treated for *Pseudomonas aeruginosa,* which was cultured from his respiratory tree and central line catheter tip. An acute pulmonary hypertensive event, possibly from a reactive pulmonary vascular bed, led to the death of patient 2; chest roentgenogram suggested early pneumonia in the right upper lobe, although cultures were negative on antibiotics. Mediastinitis did not develop in any patient in this series, although patient 1 had signs of chest wound infection as a part of a disseminated *Candida* infection.

In patient 8, increasing pericardial effusion and tamponade developed after decannulation, which was observed by echocardiography. At operation, clot was removed from the mediastinum.

Clinically significant bleeding occurred in 5 patients (36%). Three of these patients had transthoracic cannulation and 2 had femoral cannulation. One patient with carotid/jugular cannulation had substantial mediastinal drainage but did not require exploration or interruption of ECMO support. The cannulas in this infant were placed by extension of the median sternotomy incision, and ECMO was started intraoperatively. No clinically significant bleeding was encountered in patients with carotid/jugular ECMO access through a separate neck incision.

Acute renal failure was noted in 4 patients (29%). No chronic renal failure has been observed; however, dialysis or hemofiltration was used in conjunction with ECMO in 2 patients. Four patients had seizures, in 3 patients related to major neurological dysfunction and in 1 patient related to hypocalcemia. The premature infant (patient 3) had a subependymal hemorrhage before ECMO and mild and unchanging intracranial ventricular dilatation after ECMO.

Comment

Use of ventricular assist and intraaortic balloon counterpulsation devices for support of the failing circulation in adult patients who experience postoperative cardiogenic shock has become widely accepted [1–4]. Similar devices have had restricted use for infants and children after repair of congenital cardiopulmonary defects primarily due to the size limitations of current devices over the wide age and weight ranges of pediatric patients. The recognition that ECMO can provide univentricular or biventricular cardiac as well as respiratory support has extended application of ECMO to infants and children who develop refractory postoperative cardiogenic shock after repair of congenital heart defects.

Soeter and colleagues [5] first reported survival using ECMO in a young patient with acute cardiopulmonary insufficiency after correction of tetralogy of Fallot. Other reports suggested that ECMO might be a successful treatment for children with postoperative cardiac failure and potentially reversible pulmonary disease [6, 7]. Postoperative paroxysmal pulmonary hypertension after ventricular septal defect repair in an infant was successfully treated with ECMO by Cullen and associates [8]. The first larger series of patients suffering from cardiogenic shock and treated with ECMO was reported by Pennington and co-workers [9] in 1984. Four of the 14 reported patients were of pediatric age and had developed cardiac failure after operation for congenital heart disease; 3 survived

Table 3. Complications

Complication	n
Bleeding[a]	5
Transthoracic cannulation	3
Femoral cannulation	2
Neck cannulation	0
Seizures	4
Oliguria/anuria	4
Dialysis on ECMO	2
Sepsis	2
Tamponade (after decannulation)	1
Mediastinitis	0
Arrhythmias (before ECMO)	8
Junctional tachycardia	5
Supraventricular tachycardia	1
Heart block	1
Bradycardia	1

[a] Of sufficient severity to require reexploration or terminate ECMO.

ECMO = extracorporeal membrane oxygenation.

Table 4. Postoperative Extracorporeal Membrane Oxygenation

Reference	Year	Patients	Overall Survival[a]	Intraoperative ECMO	
				Patients[a]	Survival
Soeter et al [5]	1973	1	1 (100)	. . .	. . .
Bartlett et al [6]	1977	3	1 (33)	. . .	. . .
Cullen et al [8]	1986	1	1 (100)	. . .	. . .
Redmond et al [10]	1987	4	1 (25)	2 (50)	0
Kanter et al [11]	1987	13	6 (46)	1 (8)	0
Bartlett[b] [11]	1987	14	5 (36)	. . .	. . .
Trento et al [12]	1988	7	4 (57)	1 (14)	0
Weinhaus et al (present study)	1989	14	6 (36)	4 (29)	0
Total		57	25 (44)	8 (14)	0

[a] Numbers in parentheses are percentages. [b] Transcription of Dr Bartlett's discussion from the Twelfth Annual Meeting of the Western Thoracic Surgical Association, July 1986.

ECMO = extracorporeal membrane oxygenation.

after being weaned from ECMO. Redmond and colleagues [10] described use of ECMO in 5 infants with congenital heart disease and 4 pediatric patients after cardiac operation, with 60% and 50% success rates, respectively. In 1987, Kanter and associates [11] reported experience with 13 patients (4 previously reported by Pennington and co-workers) who required circulatory support with ECMO for refractory cardiac failure after repair of congenital heart disease [7]; 46% of these children survived to leave the hospital.

In our series of 14 infants and children, 64% of the patients were weaned from ECMO; these figures compare favorably with those published by Redmond and colleagues (50%) [10] and Kanter and associates (54%) [11]. In addition to the patients unable to be successfully weaned from ECMO support, there were 4 late deaths, for a 36% overall survival. A summary of the reported series of pediatric patients who required ECMO for postoperative support is presented in Table 4. Approximately 45% of reported patients survived to leave the hospital.

Whereas use of ECMO for neonates with respiratory insufficiency has been associated with a 10% to 35% incidence of neurological injury [18–21], none of our patients had intracranial hemorrhage or infarct related to ECMO, although in 1 patient cerebral infarctions secondary to disseminated *Candida* sepsis developed several weeks after the patient was weaned from ECMO support. None of the nonhemorrhagic neurosonographic findings described by Luisiri and associates [15] have been seen in our patients to date. In the neonate experience, normal intellectual outcome was noted in 64% to 71% of survivors [22, 23]. Kotogul and associates [24], however, reported only 32% of their patients as normal. All 6 survivors in our series were examined 1 to 12 months after ECMO support. Five have normal neurological evaluations, although 1 has mild gross motor delay. Growth has also been appropriate. None of the patients have residual seizure activity. There are no fundamental differences in timing or technique to explain the differences in neurological sequelae in the series of cardiac patients as compared with the neonatal respiratory patients, although the age has generally been younger in the latter group.

Hemorrhage remains a serious complication with the use of ECMO after cardiac surgical procedures. In our patients, hemorrhagic complications were frequent when the patients were placed on ECMO in the operating room without time for hemostasis and correction of coagulation deficits after cardiopulmonary bypass. The majority of hemorrhagic complications occurred in patients who had transthoracic cannulation, which may reflect the need for ECMO intraoperatively or the constant cardiac motion at the venous and aortic cannulation sites. Bleeding around the cannulation sites was the most common cause of reexploration when the transthoracic approach was used. None of the patients in this series were prematurely removed from ECMO because of excessive hemorrhage, although the magnitude of transthoracic hemorrhage was a factor in the decision for weaning from the device in patient 7, who had improvement but not resolution of pulmonary hypertension and right heart failure after heart transplantation.

Transthoracic cannulation has been the approach of choice for Pennington and Kanter and their colleagues [9, 11] even when ECMO was started in the intensive care unit. Although a substantial number of hemorrhagic complications occurred, these investigators suggested that it was simpler to reopen the sternotomy site and place transthoracic cannulas than to make a fresh groin incision and place ileofemoral cannulas. Inadequate flows have also been a problem with the groin approach.

We prefer right carotid artery and jugular venous cannulation. Attaining adequate ECMO flows (0.8 to 2.5 L/min/m^2) was not a major problem in any of the 7 patients in whom this approach was used, although venous drainage limited flow (0.85 L/min/m^2) early after initiation of support in 1 patient who had Senning atrial repair of transposition of the great vessels. With volume infusion, flow could be increased to 1.1 L/min/m^2 during the first 20 hours of support. Carotid/jugular cannulation has been used routinely for neonatal ECMO, and the transition to use in the postoperative congenital heart patients was readily made. Access was easily achieved, and severe bleeding complications did not occur in any of the 7 patients, although 1 patient who was cannulated through the neck vessels through the median sternotomy incision had marked mediastinal drainage that did not require reexploration.

It has become our practice to repair the internal jugular vein and right common carotid artery at the time of decannulation from ECMO. No immediate effects have been noted to date with this approach. Doppler neck examinations have revealed patency of the vessels 1 to 12 months after repair in surviving patients, and although 2 of the 5 patients examined had minor structural abnormalities (Fig 1), none had a flow disturbance related to the repair at the cannulation site. We hope that vessel repair will promote a more normal cerebral blood flow for the brain, which may still be recovering from postoperative insults, cardiac decompensation, or residual cardiac dysfunction, and will contribute to improved developmental outcomes. In addition, these vessels may remain patent in the event that access is needed at a later date.

Patients who require circulatory support at the time of weaning from cardiopulmonary bypass in the operating room or shortly thereafter appear to be at greatest risk of not being weaned from ECMO support (Table 1). As shown in Table 4, 8 patients in the collective reported series of patients were placed on ECMO in the operating room immediately after repair of congenital cardiac defects; none survived. Several of these patients had progressive profound hypotension and bradycardia despite good ECMO flows. Perhaps the poor results in these patients reflect more profound cardiac dysfunction that cannot be adequately supported without ventricular ejection sufficient to prevent distention. The best success in this series was obtained in cases of primarily right-sided cardiac dysfunction (Table 1). Extracorporeal membrane oxygenation is able to provide biventricular support; however, flow levels that provide full cardiopulmonary bypass may increase the afterload of the left ventricle, which is not vented during the procedure. Such preload and afterload increases may limit recovery of left ventricular function. One patient in this series (patient 14) had initiation of extracorporeal oxygenation support for biventricular failure in the operating room but had a small residual ventricular septal defect that may have decompressed the left ventricle and permitted recovery of the left side of the heart. The patient could be weaned from ECMO but subsequently died of persistent pulmonary hypertensive events. Therefore, we believe that extension of the ECMO technique with decompression of the left ventricle in cases of obvious biventricular failure is advisable and have undertaken a modification of our technique to provide this type of decompression.

As demonstrated in this series and in other reported patients, ECMO can be an effective therapy for pediatric patients with intractable low cardiac output syndrome after repair of congenital heart defects. We recommend carotid artery and jugular venous cannulation in patients who develop low cardiac output syndrome outside of the operating room. Hemorrhagic complications are reduced and long-term neurodevelopmental outcomes appear promising when right carotid artery and jugular venous cannulation and repair are performed.

This report describes an evolution of the use of ECMO for extracorporeal circulatory support. Our experience has led us to consider use of this technique in any patient who cannot be weaned from cardiopulmonary bypass in the operating room or in whom a severe refractory low cardiac output syndrome develops postoperatively. Although specific criteria for exclusion of ECMO support have not been established, procedures such as the palliative operation for hypoplastic left heart syndrome do not appear to be good procedures in which to use extracorporeal support. In the condition of single ventricle with shunt-dependent pulmonary circulation, ECMO flow may not effectively unload the ventricle because the arterial return to the patient may contribute to pulmonary overcirculation and limit systemic flow. In the 1 patient in this series in whom ECMO was used after the first-stage Norwood procedure, arterial blood pressure was not effectively supported with the technique despite improvement in blood gases. Selective use of ECMO may be most effective in such patients when severe hypoxemia occurs in the early postoperative period without hypoperfusion and ventricular dysfunction, but when the pulmonary vascular resistance may be expected to decrease with time. The problems of cannula placement in patients with a Senning intraatrial baffle repair have limited venous return in 1 patient, but we do not consider this a contraindication to ECMO. Relative contraindications to use of ECMO include severe coagulopathies or known neurologic damage.

Clearly, ECMO has been most effective in conditions of right heart dysfunction such as progressive right heart failure after operations that relieve right ventricular outflow tract obstruction. We consider the technique very valuable in patients with progressive right heart failure or transient forms of cardiac failure such as junctional tachycardias or other refractory arrhythmias that may occur in association with a low cardiac output syndrome. It may also be used for temporary respiratory support for perioperative resuscitation or tracheal repair. As more experience with the use of ECMO in the postoperative period is gained, the relative indications and contraindications for the technique may be better defined.

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Mitral Valve Reconstruction in the Elderly Population

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The technique, efficacy, and long-term results of mitral valve reconstruction have been well demonstrated and reported by Carpentier and other investigators. However, most of the results reported have been in patients aged less than 65 years. Between April 1985 and September 1988, we performed mitral valve reconstruction in 176 patients using Carpentier's classification and technique for repair. Ages ranged from 15 to 86 years (mean age, 63 years). Of the repairs, 96/176 (55%) had concomitant cardiac procedures. Patients aged 65 years or more accounted for 52% (92/176) of the population and 35% (65/176) were more than 70 years old. Hospital mortality (30 day) was 4% (4/84) in the group aged less than 65 years. Hospital mortality for the group aged more than 65 years was 12% (11/92), compared with an overall 8.5% mortality. These results suggest an increased morbidity with mitral valve repair in the patients aged more than 65 years, but this group represents an even higher risk group with mitral valve replacement.

(Ann Thorac Surg 1989;48:213–7)

Mitral valve reconstruction has engendered various degrees of enthusiasm in the United States during the past 30 years because of varied success with many types of repairs [1–5]. The relative success of mitral valve replacement with acceptable long-term morbidity has tempered this enthusiasm for mitral valve reconstruction in this country.

Not until classification and repair techniques were described by Carpentier [5] was it possible to make meaningful comparisons of groups of patients undergoing mitral valve repair. Carpentier's techniques are reproducible and teachable and continue to stand the test of time. The key to his technique is the specific classification of mitral valve dysfunction into three groups of subsequent "functional" repair, based on this classification, to return the mitral valve mechanism to normal [5] (Table 1). Because the mitral valve mechanism is maintained, left ventricular function is preserved, as was previously reported by Bonchek and colleagues [6] and more recently by Goldman and associates [7].

One of the highest risk subgroups in cardiovascular surgery today is the elderly patient with ischemic heart disease, poor left ventricular function, and mitral valve disease. Tsai and associates [8] reported a 50% mortality in their group of septuagenarians and octogenarians undergoing combined coronary artery bypass grafting and mitral valve replacement. It appears reasonable that the most up-to-date methods of myocardial protection, together with complete revascularization, should be used to treat this type of patient. Likewise, the most advantageous mitral valve procedure for left ventricular function should be used. For the past 3 years, we have used the Carpentier repair for this elderly group of patients and believe this method to be the procedure of choice.

Material and Methods

From April 1985 to September 1988, we performed 1,079 valvular procedures involving the aortic and mitral valves. There were 589 aortic valve, 434 mitral valve, and 56 double-valve procedures. Included in the group of 490 mitral procedures were 176 (36%) patients with mitral valve dysfunction treated by Carpentier's reconstructive techniques. Patients undergoing mitral valve reconstruction using techniques other than those described by Carpentier were not included in this series. Our use of mitral valve reconstruction has increased yearly since 1985 (Fig 1).

The patients ranged in age from 15 to 86 years (mean age, 63 years) (Fig 2). Patients aged more than 65 years accounted for 52% (92/176) of the mitral valve reconstruc-

Table 1. Carpentier Classification

Type	Classification
I	Normal leaflet motion
	Annular dilatation
	Leaflet perforation
II	Prolapsed leaflet
	Chordal rupture
	Chordal elongation
	Papillary muscle rupture
	Papillary muscle elongation
III	Restricted leaflet motion
	Commissural fusion
	Fused and thickened chordae

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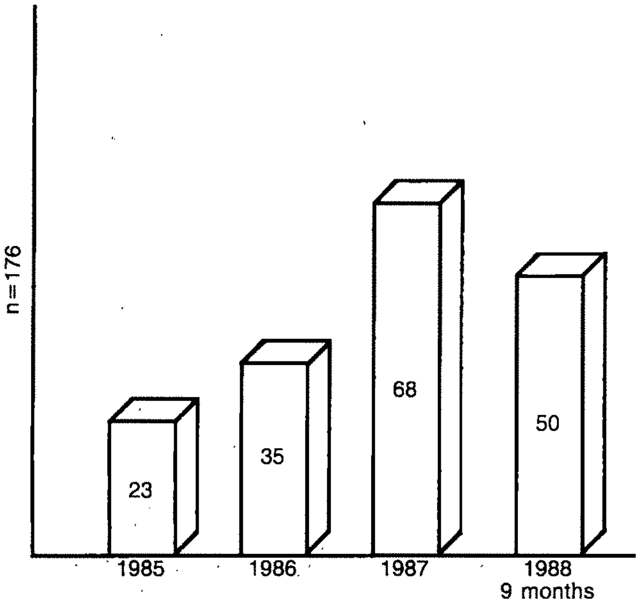

Fig 1. Incidence of mitral valve reconstruction by year.

Table 2. Preoperative New York Heart Association Functional Classification

Class	No. of Patients[a]
I	0 (0)
II	21 (12)
III	60 (34)
IV	95 (54)
Total	176

[a] Numbers in parentheses are percentages.

tions, and 35% of patients (65/176) were aged more than 70 years. There were 83 men (47%) and 93 women (53%). One hundred fifty-five patients were in New York Heart Association functional class III or IV preoperatively (Table 2).

All patients had preoperative evaluation of their mitral valve by either echocardiography, cardiac catheterization, or both. At the time of operation, direct examination of the mitral valve leaflets determined the patient's classification into either type I (normal leaflet motion with annular dilatation), type II (prolapsed leaflet), type III (restricted leaflet motion, stenosis), or a combination of the above. In our series, 34 (19%) repairs were for type I, 47 (27%) were for type II, 39 (22%) were for type III, and 56 (32%) were for combinations of types I, II, and III (Table 3).

Surgical results were obtained using many of Carpentier's mitral repair techniques either individually or in combination, depending on the valve lesion. These techniques included annular remodeling using a Carpentier prosthetic ring, quadrangular resection of the posterior leaflet with repair, chordal shortening, chordal transfer, papillary muscle reattachment, commissurotomy, annular debridement, papillary myoplasty, and cleft closure [5] (Table 4). Isolated mitral valve repair was used in 80 patients (45%), and 96 patients (55%) had mitral valve repair concomitant with other cardiovascular procedures (Table 5).

Postoperative echocardiography was obtained in as many patients as possible. In the last 3 months of this series, intraoperative esophageal color-flow Doppler echocardiography has been routinely used in all patients to evaluate the results of the mitral valve repair in the immediate postoperative period. All patients were anticoagulated with Coumadin (crystallin warfarin sodium) in the postoperative period for 2 to 3 months if in normal sinus rhythm and indefinitely if in atrial fibrillation. In several patients who had atrial fibrillation after repair, cardioversion was accomplished 2 to 3 months postoperatively, thus converting these patients to the nonanticoagulated group.

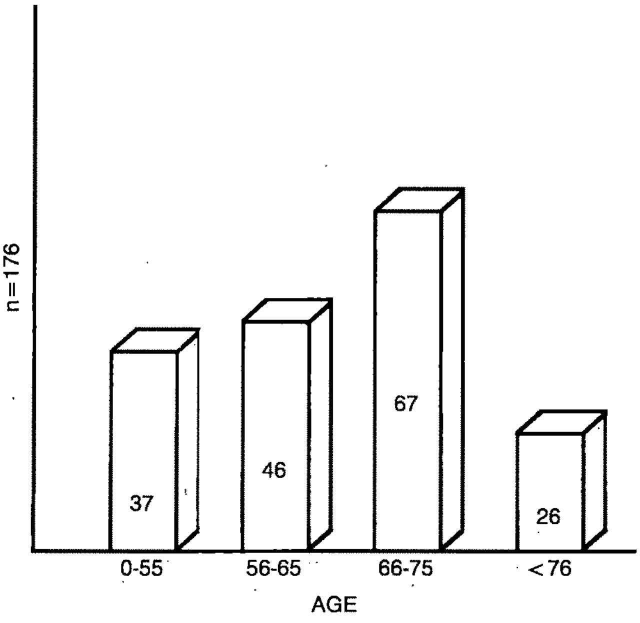

Fig 2. Age of patient population undergoing mitral valve reconstruction.

Table 3. Patient Classification

Type	No. of Patients[a]
I	34 (19)
II	47 (27)
III	39 (22)
I and II	47 (27)
I and III	3 (2)
II and III	4 (2)
I, II, and III	2 (1)
Total	176

[a] Numbers in parentheses are percentages.

Table 4. Repair Techniques

Technique	No. of Patients[a]
Ring annuloplasty	146 (83)
Quadrangular resection of posterior leaflet	51 (29)
Chordae shortening	24 (14)
Chordae transfer	3 (2)
Commissurotomy	41 (23)
Debridement	13 (7)
Papillary myoplasty	13 (7)
Cleft closure	28 (16)

[a] Numbers in parentheses are percentages.

Table 5. Concomitant Cardiovascular Procedures

Procedure	No. of Patients[a]
Myocardial revascularization	75 (78)
Aortic valve replacement	15 (16)
Aortic valve repair	2 (2)
Tricuspid valve repair + myocardial revascularization	1 (1)
Aortic valve replacement + myocardial revascularization	2 (2)
Tricuspid valve repair	1 (1)
Total	96

[a] Numbers in parentheses are percentages.

Results

There were 15 deaths within 30 days of operation, an operative mortality of 8.5%. Hospital mortality for the group aged less than 65 years was 4% (4/84), compared with a 12% (11/92) mortality in the group aged more than 65 years. Three deaths occurred in patients undergoing isolated mitral valve repair consisting of a commissurotomy. One patient died of respiratory failure, 1 died of cerebrovascular accident, and 1 died of renal and pulmonary failure. All other operative deaths occurred in patients aged more than 64 years who underwent both mitral valve repair and a concomitant cardiovascular procedure (Table 6). The single death from respiratory arrest occurred in a patient with a New York Heart functional classification less than III.

Four patients required reoperation from 2.5 weeks to 9 months postoperatively because of failure of the mitral valve repair. These were the only patients who required early or late mitral valve replacement due to failure of the mitral repair. One patient underwent successful re-repair of a dehiscence of the quadrangular resection; the remaining 3 patients required valve replacement with either mechanical or porcine valve prosthesis. Three of the 4 patients requiring reoperation for failed mitral valve repair survived their second operation.

There have been no atrial ventricular disruptions

Table 6. Operative Deaths

Patient No.	Operation	Age (yr)	Cause of Death	Postoperative Day
1	Reconstruction	36	Renal failure, respiratory failure	9
2	Reconstruction	57	Respiratory arrest	13
3	Reconstruction	58	CVA	2
4	Reconstruction + CABG	64	Respiratory failure, sepsis	1
5	Reconstruction + redo CABG + LV aneurysm	65	Pulmonary embolus, pneumonia	28
6	Reconstruction + CABG	67	Respiratory failure, acute renal failure, sepsis	6
7	Reconstruction + CABG	70	Cardiogenic shock (properative MI)	5
8	Reconstruction + CABG + LV reconstruction	72	Pulmonary failure, sepsis	25
9	Reconstruction + CABG	74	Arrythmias	3
10	Reconstruction + CABG + LV aneurysm	74	Herpes sepsis, renal failure	27
11	Reconstruction + redo CABG	74	Renal failure	2
12	Reconstruction + CABG	75	Cardiogenic shock (preoperative MI)	1
13	Reconstruction + CABG	76	Cardiogenic shock (preoperative MI)	1
14	Reconstruction + CABG	76	CVA	7
15	Reconstruction + CABG	80	CVA, renal failure, respiratory failure	9

CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; LV = left ventricular; MI = myocardial infarction.

Table 7. Preoperative and Postoperative New York Heart Association Functional Classification

	No. of Patients	
Class	Preoperative	Postoperative
I	0	74
II	13	20
III	37	6
IV	51	1

(broken hearts) in this series of patients. Two patients had postoperative murmurs of aortic outflow tract obstruction, but subsequent evaluation showed no hemodynamic significance.

Late follow-up was obtained in 124 (70%) patients either by office visit or telephone interview. Follow-up in the remaining 30% was not possible due to the nature of our patient population. Many of our patients are transient, retired individuals, who frequently change their mailing addresses, and some of the patients are from the Caribbean Islands and could not be located. Range of follow-up was 2 to 39 months. There were eight late deaths in the follow-up group. Five of the deaths were directly related to prolonged postoperative complications following the initial mitral valve reconstruction. Causes of death included respiratory failure in 2 patients, cerebrovascular accident in 1 patient, acute renal failure in 1, and pulmonary failure with sepsis in 1. One of the late deaths occurred after mitral valve replacement following failure of the mitral valve repair. Two of the late deaths occurred after hospital discharge, and the exact cause of death is unknown.

Of the 101 survivors for whom we have long-term follow-up, 94 patients (93%) were in New York Heart Association functional class I or II postoperatively. Ninety-eight patients had an improved functional class, whereas 1 remained in the same class and 2 were in a higher class (Table 7).

Comment

Enthusiasm for mitral valve reconstruction has gradually increased in the United States as surgical experience and follow-up have shown that operative mortality, long-term morbidity, and longevity are equal to and in most cases superior to mitral valve replacement [9–17]. Our patient population is similar to that of these previous reports but differs in two important aspects. The mean age of 63 years in our population is higher than that in any previous report of mitral valve reconstruction. In addition, 55% of the patients in our series had concomitant cardiovascular procedures with mitral valve reconstruction, which is a higher percentage than that in other studies in the literature [9, 10].

Our operative mortality of 8.5% is higher than those of previous reports, but if all patients aged less than 65 years old are considered separately, the mean age is 58.2 years and the mortality is halved to 4%. This is comparable with the patient population and mortalities reported by other investigators [5, 6, 10, 11]. However, 52% of our population was more than 65 years old. This group was associated with a higher incidence of (and more advanced) pulmonary disease, renal failure, diabetes, and ischemic myocardial disease. Operative mortality was 12% in this subgroup. The highest mortality (13.5%) was in patients who had combined cardiac procedures with mitral valve reconstruction; this group accounted for 55% of our patients. It is in this high-risk group that we believe mitral valve reconstruction can be most advantageous.

Although our overall mortality is higher than the excellent results reported by Spencer and associates [9], Cosgrove and colleagues [10], and other investigators [11–17], it is below comparable mortalities for mitral valve replacement reported by Tsai and associates [8] for mitral valve replacement and coronary artery bypass grafting in 70-year-old and 80-year-old patients, who account for more than one-third of our population. Our mortality for mitral valve replacement without associated procedures is 9.7% overall and 10% in patients aged more than 70 years. When mitral valve replacement is combined with coronary artery bypass grafting, our mortality is 15% for all ages and 22% in patients aged more than 70 years. In our experience, there is a clear improvement in survival in all age groups with mitral valve repair versus replacement and it is most striking in this older population. This improved survival may be due to improved left ventricular performance after mitral valve reconstruction versus replacement because of preservation of the mitral valve mechanism [6, 7].

There is no evidence in our data that deaths or reoperation for failed repairs were directly related to a learning curve; instead they were associated with the severity of the patient's underlying disease process and associated illnesses. Although with experience each surgeon became more proficient with the operation, the absence of an obvious learning curve may be due to the fact that each surgeon in his early cases operated with and under the direction of a more experienced member of the group who had observed and been instructed by Dr Carpentier at Hôpital Broussais in Paris.

The recent use of transesophageal color-flow Doppler echocardiography in mitral valve reconstruction cases has improved our ability to evaluate the repair in the beating heart before the patient is transferred from the operating room [18]. No patient in whom the intraoperative Doppler echocardiography has been used has required reoperation for recurrent mitral dysfunction. We hope that use of the esophageal Doppler echocardiography will further decrease the already low (3%) incidence of reoperation for failed mitral reconstruction in our series.

In conclusion, we believe that mitral valve reconstruction using Carpentier's stringent classification and specific techniques of repair for each group is the procedure of choice in all patients with mitral dysfunction and should be attempted in all patients. Although operative mortality will be higher in patients aged more than 65 years versus patients aged less than 65 years, mortality overall and in both subgroups will be less than in comparable patient populations who undergo mitral valve replacement. Left ventricular function is preserved with mitral reconstruction and obviously improves survival in this high-risk surgical group. The techniques of mitral reconstruction are safe, teachable, and reproducible, and the repair is durable. Mitral valve reconstruction should be considered the procedure of choice in patients of any age who undergo operation for mitral valve dysfunction with or without associated cardiovascular procedures.

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Neoadjuvant Therapy of Squamous Cell Carcinoma of the Esophagus: Role of Resection and Benefit in Partial Responders

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Twenty-eight patients were treated between 1981 and 1987 with a combination of radiation therapy and two courses of 5-fluorouracil and cisplatin followed by esophageal resection. Sixteen patients (57%) underwent resection. Operative mortality was 6% (1 of 16), and the 15 operative survivors have been followed for more than 23 months. Complete pathological response was achieved in 8 of the 15 patients, and 10 patients (66%) are alive with no evidence of disease; 4 patients (27%) have survived with no evidence of disease for more than 5 years. Four partial responders are alive, and 3 are alive with no evidence of disease for more than 5 years. An aggressive approach with a low mortality has demonstrated survival benefit to complete responders and, contrary to findings of previous reports, has established a role for surgical resection and survival benefit in patients with partial response, with 3 of 7 (47%) patients surviving more than 5 years.

(Ann Thorac Surg 1989;48:218–21)

The dismal prognosis of squamous cell carcinoma of the esophagus has persisted despite various modifications in treatment approaches. Survival rates have remained less than 10% with resection because of early lymphatic and regional spread and relatively late symptomatic presentation compounded by extensive submucosal extension and a definite risk of multicentric disease. These characteristics have limited the effectiveness of extended and more radical surgical approaches, and irradiation alone has not proved to be beneficial adjuvant therapy.

Combined chemotherapy and radiation therapy used as a preoperative adjuvant approach to carcinoma of the esophagus evolved from the experience with an adjuvant approach to squamous cell carcinoma of the anal canal [1]. This approach has proven to obviate the need for surgical resection in complete responders. Steiger and colleagues [2] reported a similar approach to squamous cell carcinoma of the esophagus in 1981 and, although early results were encouraging, long-term survival and the role of resection of the esophagus, especially in complete clinical responders (no disease on preoperative staging), has been questioned. Several additional series [3–6] have since been reported, with varied results.

In 1981, we applied the Wayne State protocol of 5-fluorouracil (5-FU), cisplatin, and irradiation followed by esophageal resection to all patients with regionally localized squamous cell carcinoma of the esophagus who were candidates for esophageal resection. Our purpose was to evaluate the feasibility and benefits of such an approach in a community referral hospital. We hoped not only to evaluate the effect on long-term survival and the morbidity and mortality associated with such a protocol, but also to determine the benefit of esophageal resection in partial responders (residual disease in the resected specimen).

Material and Methods

Between 1981 and 1987, 28 patients were shown by endoscopy, computed tomographic scans of the chest and upper abdomen, and barium swallow to have regionally localized squamous cell carcinoma of the esophagus. The ability to complete the chemotherapy and radiation therapy arms of the protocol safely, as well as evaluation of risk for esophagectomy, was determined before therapy was started. Patients were fully informed of the magnitude and uncertain benefits of the protocol. Treatment was started with a four-day infusion of 5-FU (1,000 mg/m^2) beginning on day 1 and cisplatin (100 mg/m^2) beginning on day 2, except for 2 patients who received 15 mg/m^2 mitomycin instead of cisplatin. Radiation therapy to a total dose of 3,000 cGy was started on day 1 and administered in 15 daily fractions of 200 cGy/day. A second course of chemotherapy was started on day 29 and was identical in dose and sequence to the initial course. Approximately 21 days later, patients were restaged and evaluated for their ability to undergo esophagectomy. Any patient unable to maintain nutrition was supplemented by either enteral feedings or parenteral hyperalimentation during the period of adjuvant therapy.

Patients underwent esophageal resection if no evidence of unresectable disease was found at the time of exploration or at preoperative staging. Sixteen patients under-

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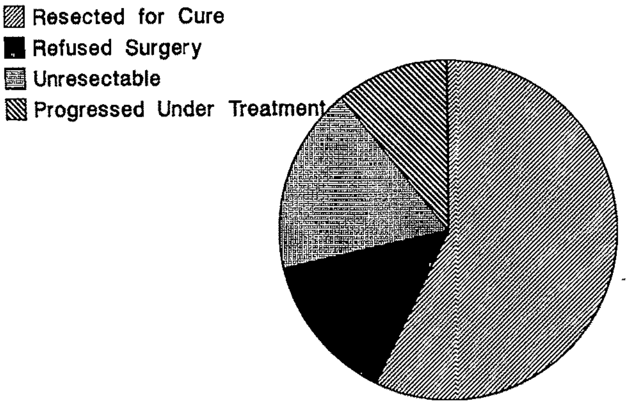

Fig 1. Fate of all patients eligible for the protocol (n = 28) demonstrates broad benefit.

went esophageal resection. Ten of the resections were performed by W.J.A. and six were performed by four other surgeons. No requirements were imposed for the surgical approach; 12 patients underwent transhiatal esophagectomy, 3 patients underwent an Ivor Lewis resection, and 1 patient underwent a standard left thoracic esophagogastrectomy. Intraoperative inspired oxygen concentrations were kept below 30% after the first 2 patients underwent operation, and any evidence of adult respiratory distress syndrome was vigorously treated postoperatively.

No postoperative adjuvant therapy was administered regardless of postresection pathological staging. All 16 patients have been followed with repeated barium swallow, a computed tomographic scan, complete blood count, and liver profiles.

Results

Twenty-eight patients were entered into the protocol and 16 (57%) underwent esophageal resection, which removed all identifiable disease. Of the remaining 12 patients, 4 refused operation and all have either died of recurrent disease or are alive with disease. Five were found to be inoperable at laparotomy and distant disease developed in 3 during postoperative adjuvant therapy.

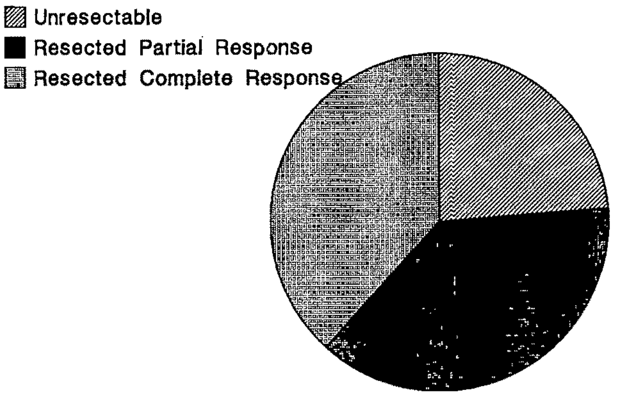

Fig 2. Most patients explored (n = 21) underwent resection for cure.

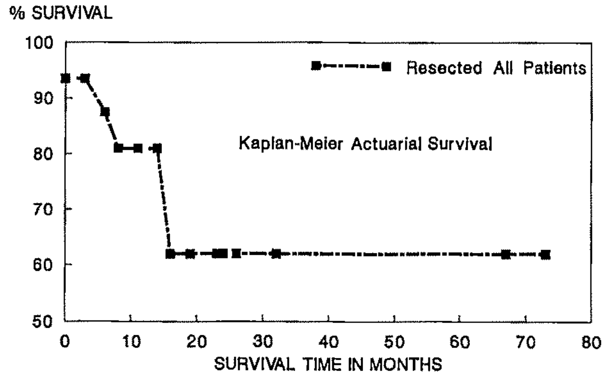

Fig 3. Survival benefits for all patients is substantial and appeared to be stable after 24 months.

One postoperative death (6%) and two suture line leaks (12%) occurred. Eight of the 16 patients (50%) had complete eradication of the neoplasm; thus, 8 of the 28 patients (29%) were classified as complete pathological responders (Figs 1, 2). Ten of these 28 patients (35%) are alive with no evidence of disease at least 23 months after diagnosis and 4 (14%) are alive with no evidence of disease at least 5 years after diagnosis.

Of the patients who underwent resection, 15 have been followed for at least 23 months (8 complete responders and 7 partial responders). In only 2 of the 15 has recurrent disease developed; these patients died at 8 and 16 months postoperatively. Two additional patients died without demonstrated recurrence at 6 and 11 months. Thus, 10 (66%) of the 15 patients who survived resection are alive with no evidence of disease at least 23 months postoperatively, and 4 of the 15 (27%) are alive with no evidence of disease 5 years after diagnosis. The median survival of all 16 patients who underwent resection assessed by probit analysis is 32.28 ± 22.6 months. Of the 7 patients with residual disease, 4 survived, and 3 of the 7 (42%) are alive with no evidence of disease more than 5 years after diagnosis. The longest survival is 83 months. Determination of actuarial survival curves (Figs 3–5) by the method of Kaplan-Meier reveals an actuarial survival for complete

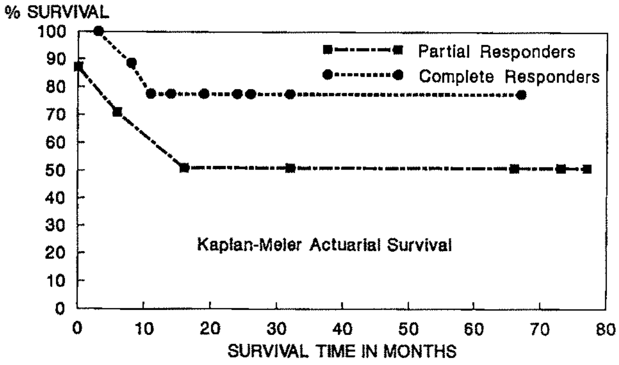

Fig 4. Although complete responders have superior survival, there is a substantial benefit for patients with residual tumor in the resected specimen.

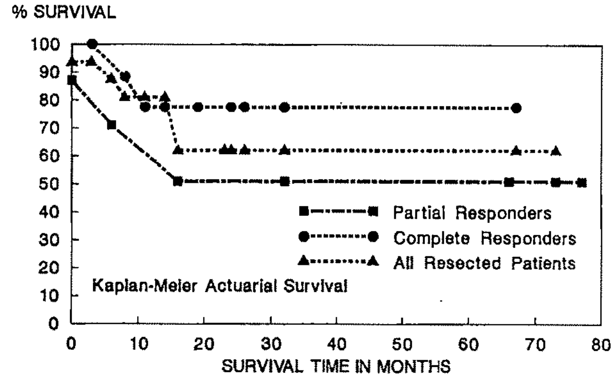

Fig 5. Response to adjuvant therapy does influence survival.

responders of 78% at 5 years. Of the 8 complete responders, only 1 patient has had disease recurrence and 1 patient died of pneumonia with no evidence of disease at 11 months. Thus, 6 of 8 (75%) complete responders are alive with no evidence of disease 14 to 67 months after diagnosis. Partial responders had a 5-year actuarial survival of 52%, and the actuarial survival of the entire group of 16 patients was 62% at 5 years.

Postoperative staging revealed 8 partial pathological responders with 2 each classified as having T1 and T2 residual disease. Four of the 16 still had T3 residual disease, 2 of whom survived at 32 and 66 months. Only 2 patients had involved lymph nodes; 1 died without evidence of recurrence at 6 months, and the other is alive without disease at 77 months.

Postoperatively, adult respiratory disease developed in 4 of 16 patients (25%), and 1 additional patient required respiratory support. All 5 patients survived after hemodynamic and ventilatory support. One of the anastomotic leaks was associated with multiple organ failure and the single postoperative death.

Comment

The inability of operation or radiation therapy alone or in combination to offer substantial hope of survival in patients with squamous cell carcinoma of the esophagus is widely accepted. The prognosis has been so dismal, combined with the natural history of the unresected lesion and the magnitude of extirpative operation, that many physicians have adopted a strictly palliative approach to treatment and have attempted to maintain the ability to swallow as the primary objective of treatment. History is replete with examples of the failure of more radical operations alone to conquer malignant disease, and such operations certainly appear to be of limited use in esophageal lesions given the pathophysiology of the neoplasm and the anatomical considerations that limit a wide lateral resection.

With the 1981 report of Steiger and colleagues [2] of a combined preoperative protocol of 5-FU, cisplatin, and radiation therapy, which eradicated the neoplasm in 30% of patients, came a fresh approach and optimism. Combined preoperative adjuvant therapy has been confirmed to be very effective in squamous cell carcinoma of the anal canal [1] as well as in some soft tissue sarcomas. The potentiation of irradiation by synchronous chemotherapeutic radiation sensitizers such as 5-FU now appears to be well founded [7, 8].

Since then, a number of series with various preoperative protocols have been reported with a variety of results [1–6]. The combination of radiotherapy and chemotherapeutic radiation sensitizers appears to be safe and practical, offering substantial potential for long-term survival. Our results in a community referral hospital clearly demonstrate that this is a practical protocol with minimal mortality (6%) and morbidity. All our patients tolerated the adjuvant therapy well, and only 2 patients required nutritional support. The potential for long-term survival benefit appears to be very promising. Eight of the 28 patients (29%) had complete eradication of the neoplasm and only 1 of these has had disease recurrence. Overall, in the last 7 years, 16 patients have completed this protocol and only 2 patients have had recurrence; 15 of the 16 patients have been followed 23 months or longer and 4 of these 15 (27%) have survived 5 years after diagnosis. Although these numbers are small, the implications of the results seem inescapable. The actuarial 5-year survival of 78% for complete responders and 52% for patients with residual disease in the resected specimen is exciting, and the actuarial 5-year survival for the entire group of 16 patients of 62% compares favorably with that of any alternative treatment protocol.

Because several series have reported that the only survivors were patients with complete eradication of the tumor by the preoperative protocol, the role of the surgical arm of this protocol has been questioned [1, 9]. Growing evidence now shows that preoperative staging of carcinoma of the esophagus is grossly inadequate. Several series have now demonstrated that 30% to 60% of patients will have microscopic residual disease even though they appear to be disease-free by current clinical staging technique [3, 10–12]. Such residual disease is probably responsible for the higher earlier recurrence rates in the absence of esophageal resection [13, 14]. Our data support the role of surgical resection. Seven of the 15 patients who underwent resection and were followed at least 22 months had residual tumor at operation, and 4 of them are alive and disease-free at 32 to 83 months of follow-up. Three of these patients (42%) are alive and disease-free more than 5 years after diagnosis. With the demonstrated low operative mortality of resection, the inaccuracy of current methods of clinical staging, and a demonstration in this series of substantial 5-year survival with residual disease at operation, elimination of the resection arm of the treatment protocol would certainly deny salvageable patients the opportunity for long-term survival. We believe that the results of the present series confirm the long-term survival benefit of this combined preoperative adjuvant therapy and establish the substantial benefit to patients with residual disease as well as the complete responders. The protocol appears to be safe and practical but requires very careful and intense attention to the medical and surgical management of the patients. Further evaluation of the preoperative phase of therapy, as well as better definition of the postoperative treatment to maximize survival benefit, will certainly improve the present results. Its application to adenocarcinoma of the esophagus and non-small cell lung cancer is being addressed in several centers.

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The Pierce-Donachy Ventricular Assist Device as a Bridge to Cardiac Transplantation

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The Pierce-Donachy ventricular assist device (VAD) was used as an attempted bridge to orthotopic cardiac transplantation in 12 patients aged 13 to 55 years. Ischemic (4 patients), dilated (4 patients), acute viral (1 patient), postpartum (1 patient), and hypertrophic cardiomyopathy (1 patient), along with a failed transplant (1 patient), were the causative factors of end-stage cardiomyopathy in these patients. All patients were candidates for orthotopic cardiac transplantation but sustained refractory cardiogenic shock (cardiac index < 2 L/min/m^2). Left VADs were placed in all patients; 7 also required right VADs. Four patients died of hemorrhagic complications less than 24 hours after VAD insertion. Ventricular assist device stabilization was successful in 8 patients and support ranged from eight hours to 64 days. Seven patients successfully underwent orthotopic cardiac transplantation. One died postoperatively of hemorrhagic complications, 6 were discharged from the hospital, and 1 patient died at 3 months of cytomegalovirus infection. Five patients are long-term survivors. The Pierce-Donachy VAD is an effective means for supporting critically ill patients with end-stage cardiomyopathy and cardiogenic shock before orthotopic cardiac transplantation. Death is related to hemorrhagic, rather than infectious or thromboembolic, complications. Patients successfully stabilized with the VAD can undergo orthotopic cardiac transplantation with acceptable mortality and morbidity rates.

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Improved survival with orthotopic cardiac transplantation (OCT) has been related to advances in myocardial preservation and more effective antirejection medication. This has led to a proliferation of cardiac transplantation programs and has resulted in a shrinking donor pool, causing increased pressure on the available recipients. Heterotopic ventricular assist devices (VADs) have helped to support the circulation in hemodynamically unstable patients who have deteriorated into cardiogenic shock [1–4]. This paper reviews our experience with the Pierce-Donachy VAD (Thoratec, Berkeley, CA) in critically ill patients who underwent VAD insertion as a bridge to OCT and recommends guidelines for VAD application.

Material and Methods

The Pierce-Donachy prosthetic ventricle is a pericorporeal pneumonic sac-type VAD placed in the heterotopic position that can maintain partial or complete circulatory support. The blood sac is made of segmented polyurethane and is enclosed in a rigid acrylic housing. Low-profile mechanical valves are used as inlet and outlet valves. Pumping action is generated by a pneumatic driver that periodically compresses the blood sac, emptying the prosthetic ventricle. The pump has a stroke volume of 65 mL and is capable of maintaining a cardiac output of up to 5.5 L/min.

The drive console can pump at a fixed rate or in a synchronous or fill to empty mode. The fill to empty mode has a variable rate, fixed stroke volume capacity. When the blood pump is full, a signal is sent to the drive console and the unit ejects blood from the blood sac. If the preload changes, the pump will fill faster or slower, changing the ejection rate. In the fill to empty mode, the drive console is autoregulatory. Rate and percentage of systole can be controlled by the console. The percentage of systole is the percentage of time the device is in systole versus diastole, which controls the filling and emptying time of the device. It is important to maintain complete filling of the blood sac to ensure that no blood clots can form within this part of the device.

The left VAD is connected to the heart by placing an outflow cannula into the ascending aorta. The inflow cannula may be placed in the left atrial appendage or left ventricular apex, or through the interatrial groove into the left atrium. The cannulas are then tunneled through the skin below the costal margin, and the device is placed on the abdomen external to the chest. A right VAD can be placed by connecting the outflow cannula to the pulmonary artery and the inflow cannula to the right atrium. Again, the cannulas are tunneled through the skin and the device is placed external to the thoracic cavity on the abdomen (Fig 1). The device can be placed while the patient is on cardiopulmonary bypass, cannulating through either the aortic arch or the femoral artery. If the

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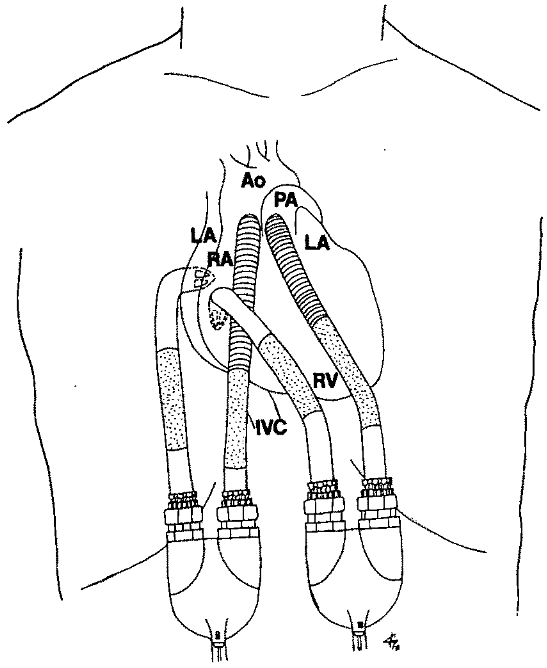

Fig 1. Pierce-Donachy biventricular assist. Left ventricular assist device inflow from the interatrial groove and outflow to the ascending aorta (Ao). *Right ventricular assist device inflow from the right atrium* (RA), *outflow to the pulmonary artery* (PA). (IVC = *inferior vena cava;* LA = *left atrium;* RV = *right ventricle.)*

patient's condition remains stable, the device can be inserted without the aid of cardiopulmonary bypass by using the interatrial groove approach. A complete description of the insertion technique for the VAD is presented elsewhere [5].

From May 1985 to June 1988, 12 patients (Table 1) who were candidates for cardiac transplantation deteriorated hemodynamically before donor hearts were procured. Eight patients were listed with the United Network for Organ Sharing as priority organ recipients, and 4 patients were admitted in critical condition and underwent immediate operation. These patients were placed on a Pierce-Donachy VAD as a bridge to cardiac transplantation. There were 10 male and 2 female patients with an age range of 13 to 55 years and a weight range of 44 to 111 kg.

All patients had been accepted as candidates for cardiac transplantation before VAD placement, and none had VAD placement after cardiotomy. Before insertion of the VAD, the average ejection fraction was 12.5%, mean cardiac index was 1.4 L/m^2, mean systolic arterial pressure was 75 mm Hg, and mean wedge pressure was 32 mm Hg (Fig 2). All patients had maximal inotropic support to maintain adequate tissue perfusion before insertion of the VADs. Three patients were intubated before entering the surgical suite, and 5 had had a previous cardiac arrest. All patients except 1 were neurologically normal before induction of anesthesia. The obtunded patient was taken to

Table 1. Clinical Characteristics and Outcome for Patients Being Bridged to Transplantation

Patient No.	Cardiomyopathy	Cannulation		Thoratec/Pierce-Donachy VAD			Cause of Death
		L-VAD	R-VAD	Duration (h)	Outcome	Complications	
1	Acute viral endocarditis	LA-AO	RA-PA	119.0	TX	Renal failure (reversible)	
2	Dilated	LA-AO	RA-PA	18.0	Death	Bleeding, respiratory failure	Shock lung, brain death
3	Hypertrophic	LA-AO	. . .	494.5	TX	Hemolysis, renal failure (reversible)	
4	Ischemic	LA-AO	. . .	4.6	Death	Bleeding, intraoperative death	Pulmonary hypertension
5	Dilated	LA-AO	RA-PA	62.0	Death	Bleeding, biventricular failure	Bleeding around cannula
6	Postpartum	LV-AO	. . .	26.5	TX	None	
7	Ischemic	LV-AO	RA-PA	58.3	TX	None	
8	Ischemic	LV-AO	. . .	20.5	TX	None	
9	Dilated	LV-AO	. . .	8.5	TX, death	Bleeding, shock lung	Bleeding, died 4 h
10	Ischemic	IAG-AO	RA-PA	777.6	Death	Infection, respiratory failure, bleeding	Sepsis
11	Failed transplantation	IAG-AO	RA-PA	360.0	Death	Bleeding	Bleeding
12	Dilated	IAG-AO	RA-PA	1536.0	TX, death	Bleeding	Cytomegalovirus sepsis, died 3 mo

IAG-AO = interatrial groove to aorta; LA-AO = left atrium to aorta; L-VAD = left ventricular assist device; LV-AO = left ventricle to aorta; RA-PA = right atrium to pulmonary artery; R-VAD = right ventricular assist device; TX = transplantation; VAD = ventricular assist device.

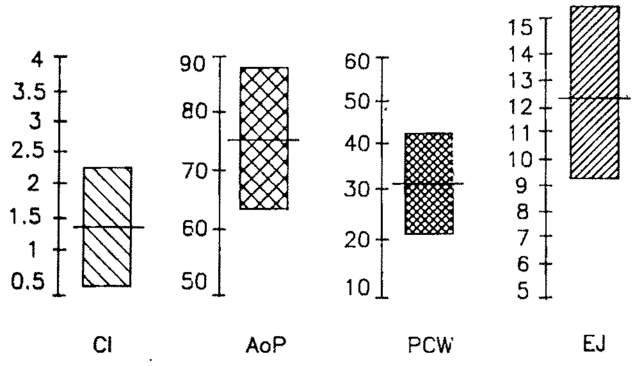

Fig 2. Hemodynamic findings in patients before ventricular assist device insertion: cardiac index (CI) (L/m²), systolic aortic pressure (AoP) (mm Hg), mean pulmonary capillary wedge pressure (PCW) (mm Hg), and ejection fraction (EJ) (%).

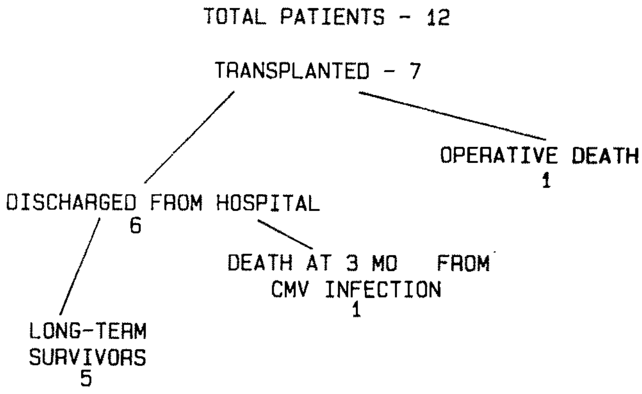

Fig 3. Patients undergoing implantation of the Pierce-Donachy ventricular assist device as a bridge to transplantation. (CMV = cytomegalovirus.)

the operating room during cardiopulmonary resuscitation.

A left VAD was inserted in all patients, and 7 also required simultaneous right VADs. Ten patients were placed on cardiopulmonary bypass, 6 through the ascending aorta and 4 through the femoral artery, before the VADs were inserted. Two patients who had the VAD placed through the interatrial groove were not placed on cardiopulmonary bypass. The VAD outflow cannulas were placed in the ascending aorta in all patients. The left ventricular inflow cannulas were inserted through the left atrial appendage in 5 patients, through the left ventricular apex in 4 patients, and through the interatrial groove in 3 patients. After the left VAD was inserted, an attempt was made to wean the patients from cardiopulmonary bypass. The right VAD was inserted in 7 patients who could not be weaned from cardiopulmonary bypass due to right ventricular dilatation, elevated right atrial pressures (greater than 20 mm Hg), and inadequate filling of the left VAD. In all patients, the direct left atrial pressure was monitored through a pressure transducer. Intravenous heparin therapy was delayed until mediastinal chest drainage was reduced to approximately 25 mL/h.

Results

Twelve patients in cardiogenic shock underwent VAD placement as a bridge to cardiac transplantation. One intraoperative death occurred due to uncontrollable bleeding in a reoperative patient who received a left VAD only. Three early deaths occurred at 15 and 18 hours and 2.6 days; all of these patients had biventricular assist devices and none received a transplant. After the VADs were inserted and the patients had stabilized, 7 patients underwent cardiac transplantation (Fig 3). Three patients had biventricular assist devices and 4 had left VADs. One patient who received a left VAD died of consumption coagulopathy 8.5 hours after transplantation. Another patient died of a cytomegalovirus infection 3 months after transplantation. The remaining 5 patients are alive and well 1 to 4 years after transplantation.

All the early deaths after insertion of the VAD were associated with excessive amounts of blood loss. Technical complications related to cannulation caused one of the deaths. In 3 other patients, uncontrolled consumption coagulopathy developed, which did not respond to medical or surgical interventions. Nonsurgical bleeding is very common after insertion of VADs. It is most important to reverse the heparin fully with titrated doses of protamine, monitoring the activated clotting times. Complete coagulation surveys, including platelet counts, prothrombin times, partial thromboplastid times, fibrinogen levels, and split fibrin products, should be performed frequently. If any of the values are abnormal, they must be corrected immediately before the patient leaves the operating room. Patients with large perioperative bleeding problems have statistically less chance of survival because bleeding rather than thromboembolism is a greater postoperative risk to life (Fig 4). Anticoagulation therapy is reserved until mediastinal chest tube drainage is reduced to approximately 25 mL/h. At this time, intravenous heparin therapy is started to maintain the activated clotting time

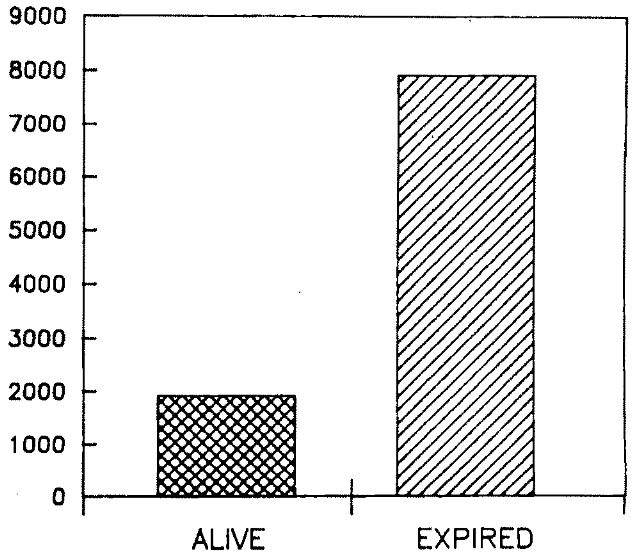

Fig 4. Mean blood loss in milliliters for first 24 hours after insertion of ventricular assist devices. Seven patients are alive and 5 are dead. ($p < 0.05$, patients who lived versus those who died.)

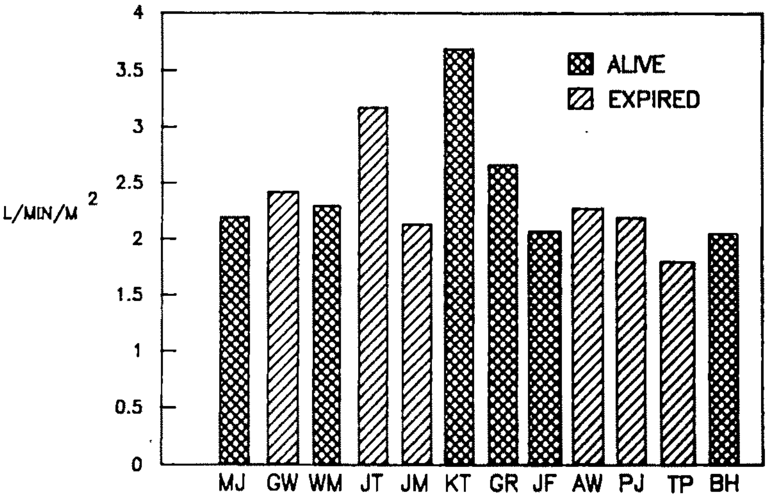

Fig 5. Mean cardiac index while on ventricular assist in liters per minute per square meter.

between 1 and 2 times control. This regimen ensures minimal likelihood of cerebrovascular embolus while the threat of uncontrolled bleeding is also decreased.

A moderate amount of hemolysis occurred in the 3 long-term patients who were VAD dependent for 21, 32, and 64 days, respectively. The plasma free hemoglobin range was from 15 to 125 mg/dL while patients were on VADs, compared with a normal range of 0 to 5 mg/dL. These patients required approximately 1 U of blood every 3 to 4 days to maintain a stable hemoglobin level. The remaining 7 patients were not on the VAD long enough for any clinically significant hemolysis to be detected.

Two technical problems were related to cannulation. In 1 patient who weighed 117 kg, the inflow cannula placed to the left atrial appendage was too short for the patient's size and caused leakage around the cannula site. This resulted in excessive blood loss, consumption coagulopathy, and death. In a second patient, the cannula was placed too deeply into the left atrium through the intraatrial groove and resulted in obstruction to the inflow of the cannula. This patient required reoperation; the cannula was withdrawn approximately 1 cm, and flow was reestablished. No difference was related to the inflow to the VADs whether the cannula was placed through the left atrium or through the left ventricle. Placing the inflow cannula either in the left ventricular apex or through the intraatrial groove rather than the left atrial appendage allowed the sternum to be closed, followed by extubation of the stabilized patient. This was a major advantage.

Although no technical problems were encountered in placing the cannula through the left ventricular apex, it is a more difficult procedure than placing the cannula through the intraatrial groove. A patient with recent infarction is contraindicated for use of the left ventricular approach. The sutures may not hold adequately in these patients, resulting in bleeding at the suture line. Two patients who had intraatrial groove inflow cannulas and whose sternums were closed were able to be extubated approximately 1 week after insertion of biventricular assist devices. These patients were able to get out of bed, sit in a chair, and eat full liquid diets. Unfortunately, both patients later became infected and required reintubation; 1 subsequently underwent transplantation and the other died of generalized sepsis.

All patients maintained normal hemodynamics while on the VAD, with an average cardiac output of 4 to 4.5 L/min. This was true whether a left VAD or biventricular assist device was inserted (Fig 5). In all 12 patients requiring circulatory support, a left VAD was inserted first. Inotropic support, dobutamine or dopamine at a dose of 10 mg/kg, was always required to wean a patient with a left VAD from cardiopulmonary bypass and usually was required, although at decreasing doses, throughout the entire VAD support period. If administration of inotropic agents was discontinued, right ventricular failure frequently followed.

A decision to insert the right VAD was made only after attempted weaning with the left VAD in place. To fill a left VAD adequately, mean left atrial pressure of approximately 15 mm Hg was required. If the right heart was unable to generate adequate filling pressures for a left VAD, or the right atrial pressure increased above a mean of 20 mm Hg, or the right ventricle became distended and contracted poorly, a right VAD was immediately inserted. A right VAD was also inserted in 2 patients who had severe preoperative ventricular arrhythmias. Both patients developed refractory ventricular fibrillation after placement of the VADs before transplantation.

Patients who have been placed on biventricular assist devices also require inotropic support during the initial postoperative period because of low peripheral vascular resistance. Moderate doses of epinephrine or norepinephrine (5 to 15 μg/kg) are required to maintain adequate perfusion. Inotropic support can usually be tapered within 48 hours of VAD implantation; patients can then remain support free. Left atrial pressures were usually maintained at 15 mm Hg to fill the left VAD adequately with appropriate fluid replacement. Pulmonary edema was easily controlled by diuresis and, in patients with biventricular support, by increasing cardiac output of the left VAD slightly over that of the right VAD. Right atrial pressures were usually maintained at a mean of 12 mm Hg in patients on biventricular assistance. These patients showed no evidence of any peripheral edema whether they had left VADs or biventricular assist devices.

Renal failure developed in 2 patients before the VADs were inserted. Both received biventricular assist devices, and 1 patient required hemodialysis while on the VAD for 5 days. The patient continued with hemodialysis after transplantation but eventually regained normal kidney function. The other patient had improvement of renal function while on the biventricular assist device; function returned to normal after cardiac transplantation. No patient without preexisting renal failure had deterioration of renal function while on a VAD. Creatinine levels remained between 1.2 and 2.5 mg/dL with blood urea nitrogen ranging from 15 to 50 mg/dL.

There were three infections after VAD placement. One was a non-VAD–related, successfully treated Legionnaires' disease at seven days after implantation. This patient later underwent transplantation and is a long-term survivor. Another patient sustained subclavian line sepsis. The Swan-Ganz catheter became entangled in the VAD cannula and was difficult to remove. Once the catheter was removed, the patient responded to treatment and underwent eventual OCT. However, this patient died of cytomegalovirus sepsis 3 months after transplantation and after discharge. The last patient developed generalized sepsis from an unknown source before transplantation.

Besides pneumonia, the most common source of sepsis is through invasive monitoring lines. Therefore, our protocol now includes changing of all central lines every four days. Swan-Ganz catheters are removed permanently as soon as the patient is hemodynamically stable, which usually occurs within the first seven days after insertion. Whenever a temperature is elevated in patients after VAD placement, we obtain a complete fever workup with blood cultures. Patients receive antibiotics throughout the entire VAD support; initial treatment consists of cephalosporins but is changed appropriately according to any positive cultures. No infections in the mediastinum or around the cannula tracts developed in these patients.

There were two neurological deficits in long-term patients on biventricular assist devices. One patient who was infected sustained embolization and a thalamic infarct was documented by computed tomographic scan approximately 35 days after VAD insertion. The patient's sepsis was treated successfully; he subsequently regained normal neurological function and underwent transplantation 64 days after VAD implantation. A second patient, who was also septic, developed a left lower extremity weakness at 19 days after implantation. The patient subsequently died of sepsis 33 days after implantation, and for his last four days was neurologically unresponsive. Both of these patients were on full heparinization at the times of their strokes. We stress that both of these patients were infected at the time of their neurological event.

After the VADs were inserted and the patients were stabilized, 7 patients underwent cardiac transplantation. Three were on biventricular assist devices and 4 were on left VADs. One patient, who received a left VAD, died of consumptive coagulopathy 8.5 hours after transplantation. Another patient died of a cytomegalovirus infection 3 months after transplantation. The remaining 5 patients are alive and well 1 to 4 years after transplantation. They are all in functional class I.

Comment

Improved results with OCT have resulted in proliferating cardiac transplant programs, increased pressure on the donor pool, and more patients deteriorating to pretransplantation cardiogenic shock [6]. We used the Pierce-Donachy VAD to intervene with these critically ill patients as a bridge to OCT.

Of the 12 patients who underwent primary VAD placement as a bridge to transplantation, 7 had OCT within one to 64 days. The 5 survivors are alive and well 1 to 4 years postoperatively. These results compare favorably with results of other investigators [2–4, 7, 8]. Patient selection after VAD placement but before OCT played a major role in eventual survival as all patients but 1 were hemodynamically, hematologically, and neurologically stable before transplantation. This led to a more efficient use of the available donor hearts with a greater chance for success.

Substantial morbidity is associated with VAD placement and includes bleeding, hemolysis, infection, stroke, and mechanical dysfunction [2, 9]. Clearly, the most important immediate problem is bleeding. Pennock and associates [1] and Farrar and co-workers [2] both reported severe bleeding with VAD placement in postcardiotomy and primary bridge to transplantation patients. Our experience mirrored these reports and showed that patients who have had previous median sternotomy and those who require extensive adhesiolysis are at great risk for severe postoperative bleeding. Two operative deaths occurred under such conditions. Ongoing long-term hemolysis by plasma free hemoglobin studies was observed in 3 patients who were VAD dependent for 21, 32, and 64 days, respectively. Other investigators [2, 10, 11] have not encountered this problem, presumably due to the short-term use of the VAD in their patients. All our long-term (>21 days) VAD patients had hemolysis and some required blood transfusions.

After hemodynamic and hematological stabilization, infection looms as the most serious impediment to successful OCT. Pennock and other researchers have emphasized the importance of avoiding sepsis in patients being bridged to transplantation [2, 8]. We have avoided cannula tract infections and mediastinal sepsis by local antiseptic wound care and continuing intravenous antimicrobial therapy. Swan-Ganz catheters are removed as soon as practical, and all central catheters are changed every 4 to 5 days. Clearly, the longer VAD patients must wait for OCT, the greater the risk for infection and death.

Clinical cerebrovascular thromboembolic complications occurred in 2 septic patients. One patient had complete resolution and subsequent successful OCT; the other died of post-VAD sepsis before OCT. Neurological events such as these have been reported by other investigators [2, 8] and remain a constant threat. In the immediate postoperative period, however, bleeding rather than thromboembolytic complications is the greater risk to life. Consequently, intravenous heparin anticoagulation therapy was delayed until bleeding was controlled. This regimen helped to minimize early bleeding complications and late cerebrovascular thromboembolic events.

Guidelines for VAD placement have been reviewed by other investigators [1–3, 12] and merit discussion. All patients with the degree of cardiogenic shock we describe require a left VAD. The decision to place the right VAD in addition to the left VAD is based on the hemodynamic data recorded during the attempted separation from cardiopulmonary bypass. Severe ventricular arrhythmias, increasing right atrial pressures (>20 mm Hg), and poorly contractile right ventricles unable to maintain left atrial pressures greater than 15 mm Hg are all indications to insert the right VAD. Pierce, Pennington, Zumbro, and their associates [3, 7, 9] have all emphasized the importance of right ventricular failure in this group of critically ill patients.

Patients who have been placed on VADs require inotropic support to be weaned from cardiopulmonary bypass. Patients with left VADs usually require dopamine or dobutamine (5 to 10 μg/kg) to provide adequate right ventricular output. Administration of these inotropic agents is usually maintained at low doses throughout the VAD period. Those patients who require biventricular assist devices also require initial inotropic support, usually epinephrine or norepinephrine (5–10 μg/kg), because of low peripheral vascular resistance. Within a few hours after the patient is weaned from cardiopulmonary bypass, the peripheral vascular resistance usually begins to increase and inotropic support can be tapered off. Our patients achieved hemodynamic stability easily on VADs with excellent perfusion, which is similar to the findings of Pierce, Pennington, Pae, and their co-workers [9–11]. Cardiac output ranged from 4 to 5 L/min with normal systemic pressures. Left atrial pressures were usually maintained at 15 mm Hg to ensure adequate filling of the left VAD with appropriate fluid replacement. Right atrial pressures were maintained at about 12 mm Hg. There was no evidence of any peripheral edema or venous congestion. Pulmonary edema was easily controlled by appropriate diuresis or by increasing left ventricular output slightly over right ventricular output.

The guidelines for OCT after VAD placement are critical to the economic and moral use of the available and shrinking donor pool. We believe that all patients should be hemodynamically, hematologically, and neurologically stabilized before OCT. One of our patients never had post-VAD, pretransplantation control of a consumption coagulopathy. He underwent OCT shortly after VAD placement but the coagulopathy never resolved and he died of uncontrollable hemorrhage. Clearly, this patient would have profited from more time to stabilize, whereas another patient may have benefited from the donor heart. The dilemma of concomitant post-VAD, pretransplantation organ failure requires careful evaluation. Potentially reversible organ failure is not a contraindication to OCT, as we had 1 patient who required renal dialysis while on VAD support but had successful OCT with return to normal renal function. However, one must use careful and prudent judgment in evaluating these critically ill patients realistically before OCT.

The long-term survival of these patients should reflect the survival rates of non-VAD OCT patients. Optimal stabilization of VAD patients before transplantation [2, 7, 8, 12] will ensure an efficient use of donor hearts with acceptable mortality and morbidity rates. Our 5 surviving patients are in class I and are indistinguishable from other transplant patients.

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Gentamicin Solution for Mediastinal Irrigation: Systemic Absorption, Bactericidal Activity, and Toxicity

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Local irrigation with gentamicin sulfate represents a possible substitute for neomycin sulfate, used for many years but now no longer available for use as an irrigation fluid. In this investigation, mediastinal irrigation with gentamicin was used in 12 patients who had experienced problems after a heart operation. The regimen employed for mediastinal irrigation with gentamicin was equipotent with that using neomycin. We sought to determine the degree of absorption and risk of either inadequate or toxic blood levels that might follow gentamicin absorption. Irrigation periods were short, ranging from one to four days and determined by measurements of plasma gentamicin concentration using radioimmunoassay evaluation. Systemic gentamicin absorption occurred in all patients. Toxic levels of higher than 8.0 μg/mL occurred and were size related, ie, correlated with smaller body weight and surface area, and sex related, ie, female sex. Larger-sized patients often had inadequate levels. Despite the potential risk from toxic blood levels, major increases in serum creatinine levels were not seen. These findings suggest that monitoring of plasma gentamicin levels during mediastinal irrigation with gentamicin is mandatory to avoid both inadequate treatment and toxicity.

(Ann Thorac Surg 1989;48:228–31)

Clagett and Geraci [1] introduced the use of neomycin sulfate irrigation using a 0.25% concentration in saline solution for the treatment of postpneumonectomy empyema in 1963. Despite its risk of ototoxicity, nephrotoxicity, and neuromuscular blockade [2, 3], irrigation of the mediastinum with neomycin solutions has been used for many years for the prevention and treatment of mediastinitis after cardiac procedures [4–6]. In such instances, one or both pleural cavities can be open and tissue surfaces are usually inflamed, circumstances predisposing to systemic uptake of the drug [6, 7]. Neomycin was not designed for parenteral use, and laboratory assays for measuring its concentration in blood are difficult to perform. In this decade, courts have held that irrigation with neomycin solutions is unacceptable without the monitoring needed to avoid toxic blood levels [8]. Consequently, its manufacture in parenteral form has been discontinued.

Gentamicin sulfate may be an acceptable alternative to neomycin if an aminoglycoside mediastinal irrigation solution is clinically indicated. Compared with neomycin, gentamicin possesses a similar antibacterial spectrum, is less toxic, less expensive when mixed in equivalent concentrations, ie, 800 mg of gentamicin in 1.0 L of normal saline solution, a 0.08% solution with 800 μg/mL versus neomycin 0.25% (2.5 g/L), and equally diffusible [7]. In addition, the assay for gentamicin concentration in blood is easy to perform [9–11]. At Emory Hospital, when parenteral neomycin was discontinued, it was replaced by this gentamicin solution, similarly used at rates of 100 mL/h [1], when indicated for mediastinal irrigation.

This retrospective study sought to determine (1) whether gentamicin solution used in the same fashion as neomycin for mediastinal irrigation could produce blood levels of sufficient magnitude to be measured clinically; (2) whether these levels might reach the toxic range; and (3) what factors might predispose to increased gentamicin absorption, as guidelines for the use of gentamicin irrigation of the mediastinum are not available.

Material and Methods

Records of patients requiring irrigation of the mediastinum with gentamicin were reviewed to determine whether toxic levels of gentamicin or changes in creatinine levels had occurred, and to see whether these levels were related to sex, body weight, or body surface area (BSA). The 12 patients, 6 men (mean weight, 78.4 ± 8.06 kg) and 6 women (mean weight, 65.7 ± 10.8 kg) aged 40 to 75 years, had mediastinal irrigation with a 0.08% gentamicin solution at a rate of 100 mL/h after admission to the intensive care unit. All patients had undergone coronary artery revascularization, and 3 had had a valve procedure as well. The perioperative course was marked by major hemodynamic instability, accompanied by either reexploration or failure to effect chest closure. Bleeding

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was not excessive at the time gentamicin irrigation of the mediastinum was begun.

Nephrotoxicity was defined as a rise in the baseline serum creatinine level of at least 30% during or after the infusion period.

Samples for plasma gentamicin assay were drawn before the initiation of irrigation and at the following times during gentamicin infusion: 8, 16, 24, and 36 hours. In 2 of the patients, irrigation was continued for an additional 48 hours, and levels were further determined at intervals of 12 to 24 hours until the infusion was discontinued. After discontinuation of the infusion, blood samples were drawn at 1, 4, 12, and 24 hours to assure drug clearance.

Gentamicin samples were drawn from an indwelling arterial catheter, saved in 5.0-mL unheparinized tubes, and immediately centrifuged at room temperature with the serum removed and stored at −70°C for later analysis. Blood gentamicin levels were assayed using a fluorescence polarization immunoassay (Abbott TDx System; Abbott Diagnostics, Irwing, TX), a method widely used for monitoring antibiotic therapy with an error of ± 5.0% in the clinical range of concentrations [12]. Guidelines for parenteral use of gentamicin are readily available, and have as accepted target levels a peak of 8.0 µg/mL and a trough of 2.0 µg/mL [13]. Similar guidelines for neomycin are not available. Plasma gentamicin levels were reported 18 to 24 hours after the sampling time. Infusions were slowed to 50 mL/h or stopped if levels higher than normally accepted peaks, ie, 8 µg/mL, were seen.

The significance ($p < 0.05$) of differences in mean plasma concentration of gentamicin with respect to sex, weight (>70 kg versus <70 kg), and BSA (>1.75 m^2 versus <1.75 m^2) during the course of the gentamicin irrigation were determined with t tests and the significance of the increases in serum creatinine levels, with paired t tests.

Results

By 16 hours of irrigation, a size-related effect was evident. Five of the 6 women and 1 older man (patient 7, 72 years old) had plasma gentamicin levels greater than 8.0 µg/mL (Table 1). In contrast, 3 of the men failed to reach a therapeutic level of 2.0 µg/mL. Patients with a BSA less than 1.75 m^2 had significantly higher mean gentamicin levels than those with a BSA greater than 1.75 m^2 (Fig 1). Because BSA, weight, and sex were interrelated, mean gentamicin levels were also significantly different in those patients whose body weight was less than 70 kg versus those whose weight was greater than 70 kg (Fig 2), and similarly, female patients, 5 of the 6 of whom were in the lower weight and smaller BSA group, had significantly higher mean plasma gentamicin levels than their male counterparts (Fig 3).

Table 1. Gentamicin Levels With Irrigation

Patient No.	Sex	Weight (kg)	Body Surface Area (m^2)	Plasma Gentamicin Levels[a]				
				Time After Starting Irrigation				
				Start	8 h	16 h	24 h	36 h
1	M	73	1.65	1.8	1.6	1.7	1.9	3.4
2	M	79.5	2.01	7.8	4.6	3.7[b]	1.7	0.7
3	F	52	1.51	0.4	10.2	11.8[b]	12.6	ND
4	M	72	1.71	0.1	0.7	1.3	1.0	2.0
5	F	68	1.70	0.7	19.6	26.4[b]	32.0	22.0
6	F	63	1.66	3.5	14.1	15.2[b]	15.8	14.3
7	M	79	2.01	1.4	8.7	11.2[b]	7.0	3.9
8	F	84	1.89	1.3	1.0	0.9	1.0	0.8[b]
9	F	59	1.63	5.3	15.2	13.4	12.7	17.5[b]
10	M	72	1.93	0.4	1.0	1.6	1.7[b]	0.9
11	M	95	2.10	ND	3.0	4.4	5.4	5.1
12	F	68	1.65	ND	6.6	12.4	14.0	12.6[b]

[a] Data are shown in micrograms per milliliter. [b] Irrigation was halted.
ND = not drawn.

When gentamicin irrigation was stopped, levels fell with reasonable rapidity, as illustrated by the case of 1 patient (patient 6) who had high gentamicin levels (Fig 4).

Mean serum creatinine values rose significantly with irrigation (Table 2). The change from the mean preoperative value to the mean value on postoperative day 1 was compared using paired t tests: the difference, 1.25 to 1.72 was significant ($t = 4.0$, $p < 0.005$). The change between the mean preoperative value and the mean value on postoperative day 2 was similarly compared: the difference, 1.25 to 1.85, was also significant ($t = 3.8$, $p < 0.005$).

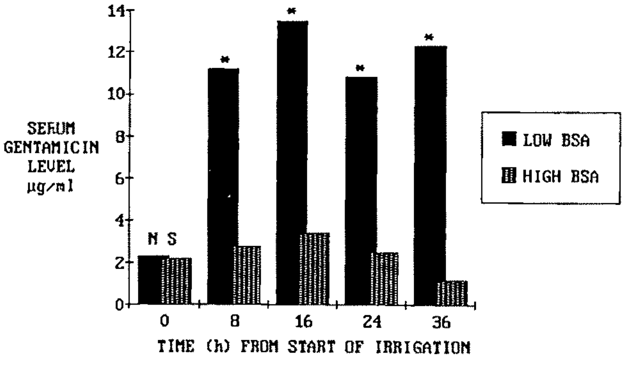

*Fig 1. Body surface area (BSA) versus gentamicin sulfate levels. (NS = not significant; * = $p < 0.05$.)*

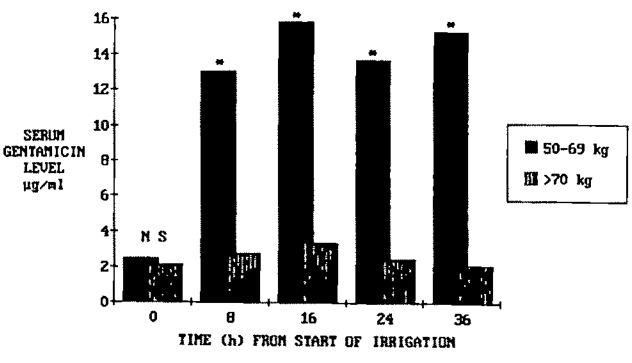

*Fig 2. Weight versus gentamicin sulfate levels. (NS = not significant; * = $p < 0.05$.)*

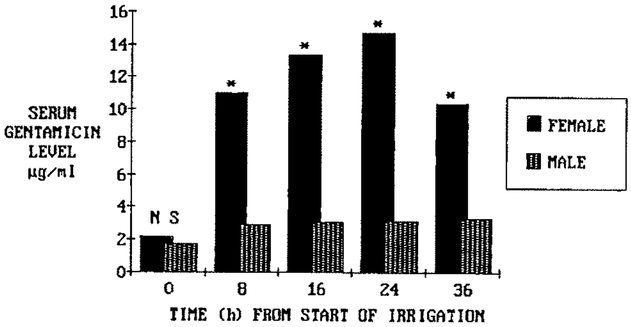

Fig 3. Sex versus gentamicin sulfate levels. (NS = *not significant;* * = p < *0.05.)*

No deaths occurred as a result of renal dysfunction, and all of the patients who survived had normal or nearly normal creatinine values by the end of the study period.

Two of the 12 patients died. Purulent mediastinitis with a gram-positive organism developed in another patient.

Comment

Despite the known hazards, irrigation with aminoglycoside antibiotics is widely used and considered indicated in patients with mediastinitis [4, 5]. Failure to monitor blood levels as part of the attempts to avoid toxic complications is now considered negligent [8]. Monitoring the plasma concentrations of neomycin is difficult; consequently, this drug is no longer available for mediastinal irrigation. This has created the need for a drug that has similar characteristics and can be easily monitored. For this study, we used the aminoglycoside gentamicin. Patients underwent gentamicin mediastinal irrigation using a similar flow rate (100 mL/h) and potency (0.08%) as used for many years with neomycin.

Systemic absorption of gentamicin occurred in all patients. Like peritoneal dialysis, absorption and transfer of the drug across the membrane surfaces of the mediastinum were usually enough to produce adequate systemic gentamicin levels. The resultant plasma gentamicin concentrations were insufficient to produce a therapeutic effect, ie, less than 2 µg/mL, in some patients but were toxic in others, who showed rapid rises to blood levels that reached and remained higher than the accepted peaks for conventional systemic gentamicin therapy. Toxic levels were associated with female sex, lower weight, and smaller BSA. Adjustment, upward or downward, of the irrigation flow rate was necessary in many of the patients to avoid the extremes of both inadequate therapy or gentamicin toxicity.

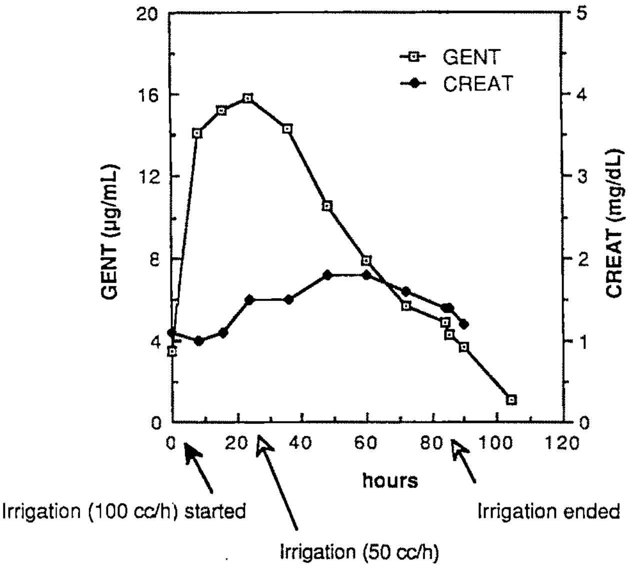

Fig 4. Gentamicin sulfate (GENT) and creatinine (CREAT) levels in a typical patient with a small body surface area.

Table 2. Creatinine Levels With Irrigation

			Body	Serum Creatinine Levels[a]				
			Surface	Time After Starting Irrigation				
Patient No.	Sex	Weight (kg)	Area (m^2)	Preop	POD 1	POD 2	POD 3	POD 4
1	M	73	1.65	1.3	2.0	1.8	ND	1.7
2	M	79.5	2.01	1.3	2.1	2.7[b]	2.2	1.7
3	F	52	1.51	1.7	2.6	2.8	Died	. . .
4	M	72	1.71	1.3	ND	1.3	1.4	1.6
5	F	68	1.70	1.2	2.2	Died	. . .	. . .
6	F	63	1.66	1.0	1.5	1.8	1.4[b]	1.2
7	M	79	2.01	1.4	1.2	1.6[b]	ND	ND
8	F	84	1.89	1.1	1.3[b]	1.5	1.9	1.4
9	F	59	1.63	1.1	1.6[b]	1.9	1.7[c]	1.3
10	M	72	1.93	1.2	1.4	1.3	. . .[b]	ND
11	M	95	2.10	ND	2.9	2.3	2.0	1.7
12	F	68	1.65	1.1	1.3	1.3[b]	1.4[c]	1.2

[a] Data are shown in milligrams per deciliter. [b] Irrigation was halted. [c] Irrigation was started again.

ND = not drawn; POD = postoperative day.

The irrigation periods were all short term. Although statistically serum creatinine levels rose to a moderate degree, the increase in the survivors was reversible, and clinically significant nephrotoxicity [10, 14] did not develop. However, it is obvious that for prolonged periods of irrigation, safe tissue concentrations are necessary. Therefore, monitoring with a target for blood gentamicin levels near accepted troughs is essential to minimize risks.

We conclude that gentamicin, 0.08% in normal saline solution, can safely be used for mediastinal irrigation in patients at risk for mediastinitis. However, the irrigation flow rate should be based on BSA, as clinically significant systemic absorption can occur. Furthermore, monitoring of plasma gentamicin levels is essential both to assure adequate therapeutic levels and to avoid potential toxicity.

Richard I. Hall is a Merck Sharp & Dohme International Fellow in Clinical Pharmacology.

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Prevention of Arrhythmias by Flecainide After Noncardiac Thoracic Surgery

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Cardiac arrhythmias are a frequent complication after thoracic operations. The prophylactic value of flecainide administered as a constant-rate, intravenous infusion (0.15 mg/kg/h) after a loading dose (2 mg/kg) was tested in a randomized, placebo-controlled study in 30 patients using Holter monitoring during the first 72 hours after operation. A high incidence of atrial and complex ventricular arrhythmias was observed in the placebo-treated group, with a clear predominance in patients undergoing left thoracotomy. Antiarrhythmic drugs had to be added in 6 patients in the placebo-treated group (n = 16), but in none in the flecainide-treated group (n = 14) ($p < 0.01$). The preventive effect of flecainide was observed at serum concentrations in the middle of the therapeutic range (409 ng/mL) without side effects. It is concluded that flecainide administration effectively reduced or prevented cardiac arrhythmias after thoracic operations.

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Cardiac arrhythmias, of both ventricular and supraventricular origin, are a well-recognized complication after noncardiac thoracic operations [1, 2]. Only digoxin has been extensively studied as a prophylactic antiarrhythmic drug in this clinical setting, but its value in this indication remains controversial [3]. The efficacy of flecainide, a new type Ic antiarrhythmic agent, in treating both ventricular and supraventricular arrhythmias has been demonstrated [4, 5]. To our knowledge, its prophylactic value has not yet been ascertained. Therefore, our study was aimed at determining the type and frequency of arrhythmias and the value of flecainide in preventing cardiac arrhythmias during the first 72 hours after a noncardiac thoracic operation. This period of monitoring was chosen because it has been reported that more than 60% of the arrhythmias appear during the first three postoperative days [6].

Subjects and Methods

Inclusion and Exclusion Criteria

Patients eligible for elective noncardiac thoracic operation were allowed to enter the study if they had no severe cardiac failure (stage III or IV according to the New York Heart Association classification), atrioventricular block (Mobitz type I or II, complete atrioventricular block), bifascicular block or bundle branch block, sick sinus syndrome, unstable angina pectoris, history of myocardial infarction within 12 weeks of the start of the study, known allergy to flecainide, or hepatic (aspartate aminotransferase or alanine aminotransferase level > 3 times the normal values) or renal failure (plasma creatinine level > 300 μmol/L) and were not taking antiarrhythmic drugs, calcium antagonists, or digitalis. The study was approved by the Ethics Committee of our institution. Informed consent was obtained from all patients.

Study Design

Thirty consecutive patients meeting the inclusion criteria and without any exclusion criteria were randomly allocated in a single-blind fashion to one of two groups. Rhythm monitoring was performed with the Holter technique before and after operation during periods of from 24 up to 72 hours. Automatic and manual analysis of tapes was done without knowledge of the patients' condition.

After admission to the surgical intensive care unit, group A patients received an infusion of flecainide (2 mg/kg) over 60 minutes as a loading dose, followed by a maintenance infusion at a rate of 0.15 mg/kg/h, calculated to produce serum concentrations in the middle of the therapeutic range, up to the end of the study. Group B patients received an infusion of normal saline solution (placebo). Blood samples were drawn at the end of the loading dose, at 4 and 12 hours of the start of the maintenance infusion, and every 12 hours thereafter up to 72 hours. Urine samples were collected at eight-hour intervals during the first 24 hours and at 12-hour intervals thereafter for flecainide concentration measurement.

Concurrent Treatment

Postoperative analgesia was provided by a constant intravenous infusion of morphine (2 to 5 mg/h) or by the administration of morphine (3 mg) through a peridural catheter. When present, hypertensive episodes were treated either by nitrates, sodium nitroprusside, or phentolamine. Digitalization was undertaken if heart failure remained uncontrolled by diuretic agents (furosemide or ethacrynic acid) and peripheral vasodilators. Arrhythmias were treated in either group if frequent complex ventric-

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ular arrhythmias (Lown type IV or V) developed or if supraventricular arrhythmias were accompanied by alterations of the ST segment or were hemodynamically poorly tolerated. Plasma potassium level was maintained between 3.6 and 4.5 mmol/L by an intravenous infusion of potassium chloride. The patients were mechanically ventilated for six to 24 hours; weaning was performed using the synchronous intermittent mandatory ventilatory technique. Patients were questioned twice daily about the appearance of side effects.

Evaluation of the Results

Electrocardiographic monitoring was performed with a two-channel Marquette 8500 electronics recorder. Tapes were scanned on a Marquette Laser-Holter monitor for detecting and quantitating supraventricular and ventricular arrhythmias. All tapes were also reviewed manually by one of the investigators (A.B.). Serious arrhythmias were defined as follows: (A) ventricular: complex ventricular arrhythmias graded according to Lown criteria (IVa = couplets; IVb = ventricular tachycardia; V = R on T phenomenon); (B) atrial: atrial fibrillation or flutter, paroxysmal supraventricular tachycardia. Episodes of paroxysmal supraventricular tachycardia were defined as an atrial rate greater than 100 beats/min and a cycle length at least 15% faster than the basic sinus rhythm, with abrupt onset and termination and a P wave morphology distinctly different from sinus P wave. Treatment failure was defined as the need for increasing the dose or introducing a new antiarrhythmic drug.

Flecainide levels in serum and urine were determined by high-pressure liquid chromatography with ultraviolet detection. Systemic clearance of flecainide was calculated as the rate of infusion divided by the serum concentration at steady state (mean of the measured serum concentration at the plateau). Renal clearance was calculated as the amount of flecainide excreted divided by the area under the serum concentration-time curve. The area under the serum concentration-time curve was calculated by the trapezoidal rule [7].

Statistical evaluation of the results was done using Fisher's exact test or the χ^2 or the Mantel-Haenszel χ^2 methods [8, 9]. Results are given as mean ± standard error of the mean.

Results

Patients in groups A (flecainide; n = 14) and B (control; n = 16) were comparable in terms of age (51 ± 5 years [range, 19 to 72] versus 59 ± 3 [range, 44 to 71]), underlying disease (neoplasias, 11 versus 13; tuberculosis, 2 versus 1; secondary to an infectious pleural effusion, 1 versus 2), and type of surgical procedures (Table 1).

Table 1. Distribution of Surgical Procedures

	Flecainide Group		Control Group	
Type of Operation	Right	Left	Right	Left
Lobectomy	4	5	6	4
Bilobectomy	2	. . .	. . .	. . .
Pneumonectomy	1	. . .	1	. . .
Pleural decortication	. . .	2	1	2
Other	. . .	. . .	1	1

Table 2. Treatment Failure Distribution According to Treatment and Side of Thoracotomy

	Flecainide Group		Control Group	
Variable	Right	Left	Right	Left
Number treated	7	7	9	7
Number of failures	0	0	1	5

No treatment failure was observed in group A, whereas 6 patients in group B had to receive an antiarrhythmic drug ($p < 0.05$; Table 2): 3 patients because of complex ventricular arrhythmias and the 3 others because of atrial fibrillation hemodynamically poorly tolerated. Even after excluding these 6 patients, the number of premature ventricular contractions per hour and per patient was significantly decreased in group A compared with group B ($p < 0.05$) (Fig 1). In addition, there was a tendency toward a decrease in the number of paroxysmal supraventricular tachycardias in group A (0.1 versus 1.0 per patient per day). Complex ventricular arrhythmias (Lown type IV and V) were observed in 10 patients (33%); 2 in group A (2/14) and 8 in group B (8/16) ($p < 0.05$).

Considering the effect of the side of the thoracotomy on the incidence of arrhythmias, no difference was observed between left and right thoracotomy in group A. In contrast, a significant increase in the incidence of arrhythmias was noticed in group B patients with left thoracotomy (Table 2).

The constant-rate flecainide infusion resulted in mean steady-state plasma levels of 409 ± 67 ng/mL. The systemic and renal clearance rates of flecainide were 499 ± 55 mL/min (7.4 ± 1.0 mL/kg/min) and 123 ± 15 mL/min (1.9 ± 0.2 mL/kg/min), respectively. No side effects related to this low-dose flecainide infusion were observed.

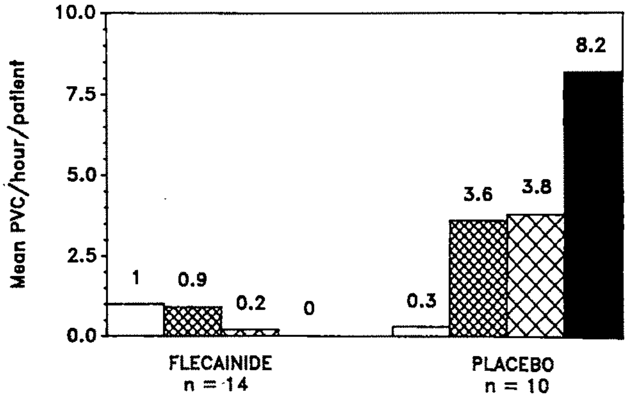

Fig 1. Mean premature ventricular contractions (PVC) *per hour per patient in treated and control groups.* (Open box = *before operation;* narrow cross-hatch = *day 1;* wide cross-hatch = *day 2;* solid box = *day 3 after operation.*)

Comment

This study demonstrated a very high incidence of atrial and ventricular arrhythmias after thoracic operations. Previous studies [6, 10, 11] have shown an incidence of dysrhythmias after noncardiac thoracic operations ranging from 3% to 40%, appearing mostly during the first three days after operation [6]. Supraventricular arrhythmias, atrial fibrillation in particular [6, 11], have been most often described. Little information is available concerning the number and severity of ventricular dysrhythmias. Ghosh and Pakrashi [2] have reported the appearance of a low incidence of premature ventricular contractions after thoracotomy. The unexpected high incidence (33%) of complex ventricular arrhythmias (Lown type IV or V) found in our study is probably explained by differences in monitoring techniques among the previous studies and our study: either 12-lead electrocardiographic preoperative and postoperative recordings [6, 10, 11], routine continuous electrocardiographic monitoring [12], or continuous Holter monitoring, as in our study. Indeed, it has been shown that the number of ventricular arrhythmias in the coronary care unit were underestimated by continuous electrocardiographic monitoring compared with Holter monitoring [13].

We found an increased incidence of arrhythmias in patients undergoing left thoracotomy. This is in accordance with the results previously reported by Mowry and Reynolds [6]. Moreover, the importance of the operative side is highlighted by the higher failure rate observed in the placebo-treated group undergoing left thoracotomy.

The beneficial effect of flecainide infusion as compared with placebo in preventing both atrial and ventricular dysrhythmias was striking. As Krowka and co-workers [12] recently reported that tachydysrhythmia after pneumonectomy is associated with significant mortality, our findings, albeit in a small group of patients, have clear clinical relevance. However, the value of flecainide in decreasing the mortality rate was not addressed by our study and remains to be evaluated. Similarly, its value in preventing morbidity after thoracotomy still needs to be assessed.

Digoxin has been the only drug extensively studied in the prevention of arrhythmia after thoracic operations, but its role remains controversial. Some investigators found it beneficial [10] and others of no benefit [3]. Therefore, we decided to compare the effects of flecainide prophylaxis with placebo.

The protective effect of flecainide was afforded at serum concentrations in the middle of the previously reported therapeutic range [14, 15], and was not associated with any adverse effect. The renal clearance of flecainide was slightly lower in our patient population than observed in normal volunteers [14]. The systemic clearance of flecainide, however, was not appreciably different from previously reported values [14]. These results suggest that the immediate postoperative period itself is not associated with clinically significant alterations in flecainide disposition.

In conclusion, constant rate, intravenous infusion of flecainide administered during the three days after thoracic operation reduced or prevented cardiac arrhythmias, in comparison with a control group, without any side effects.

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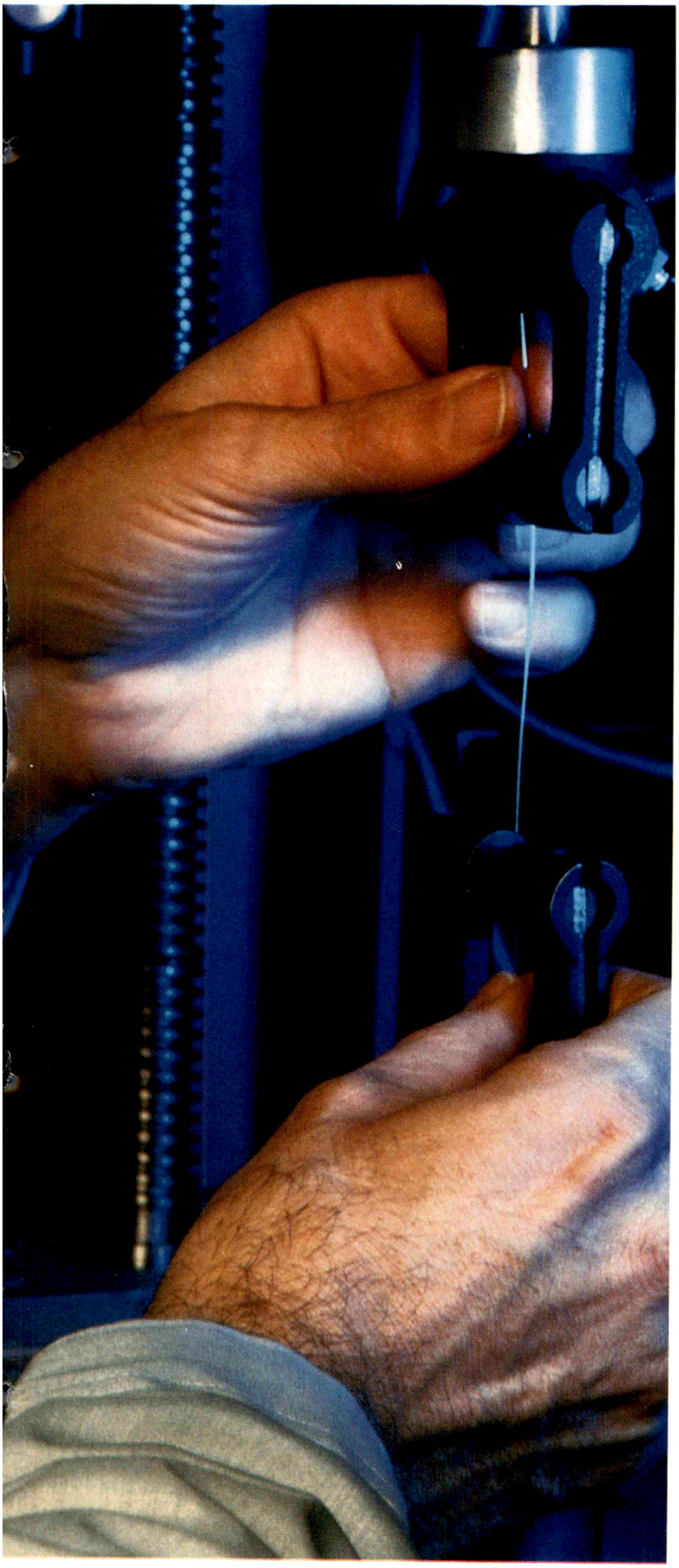

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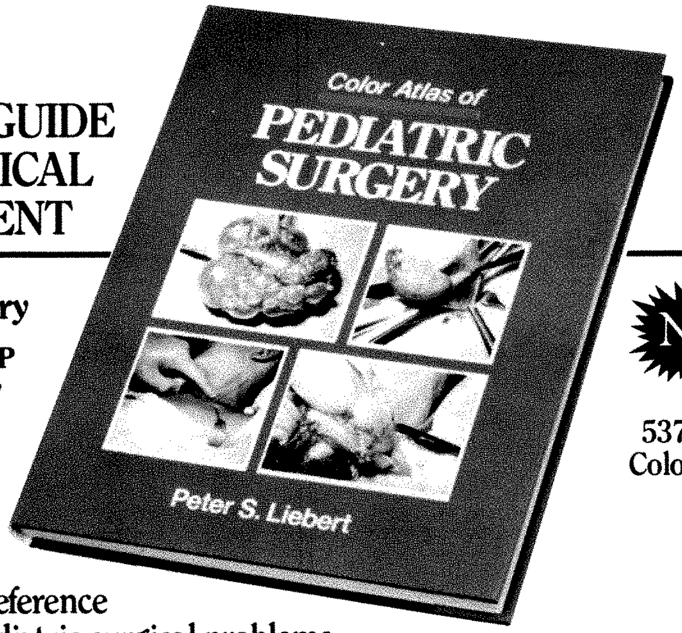

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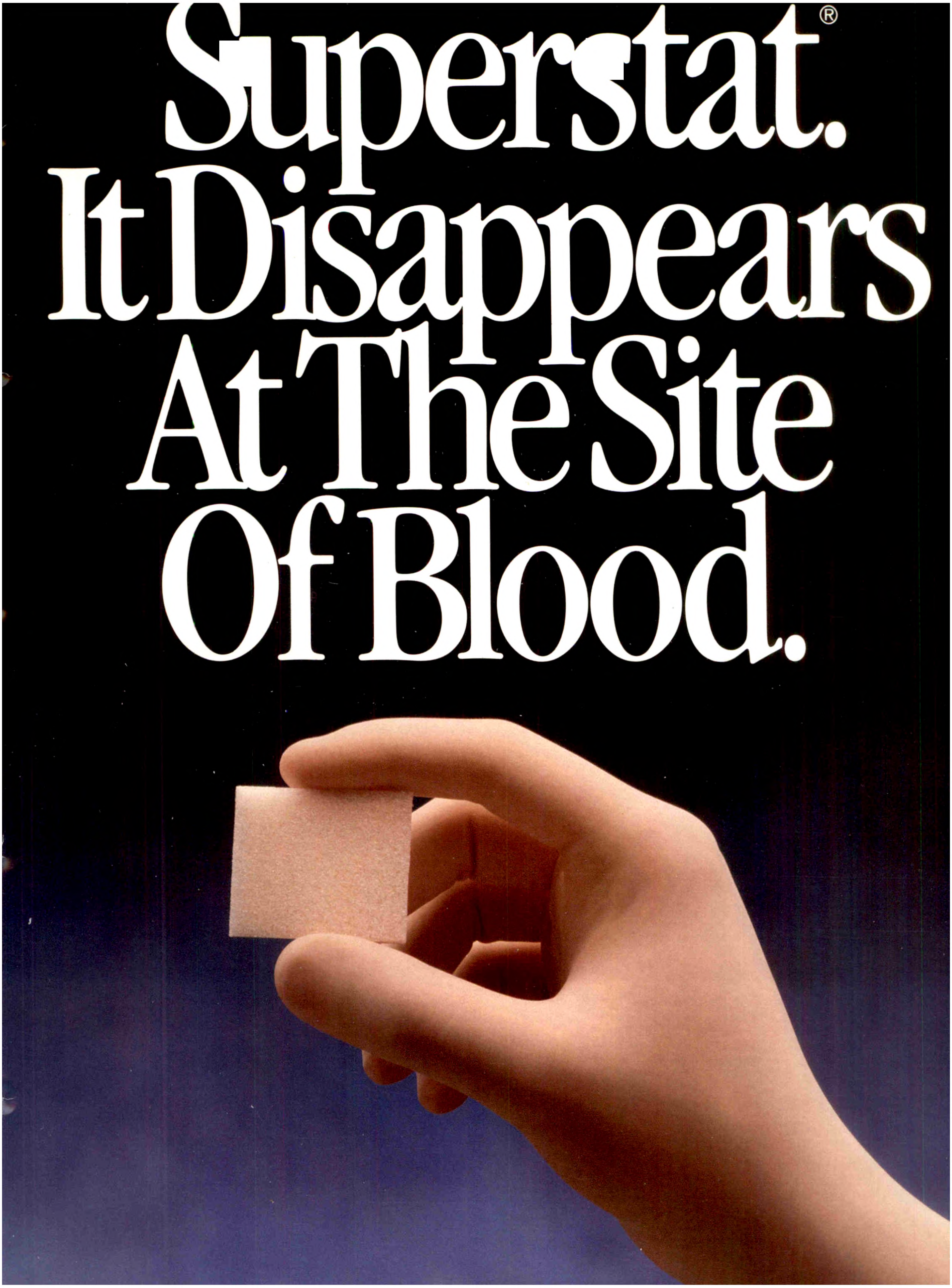
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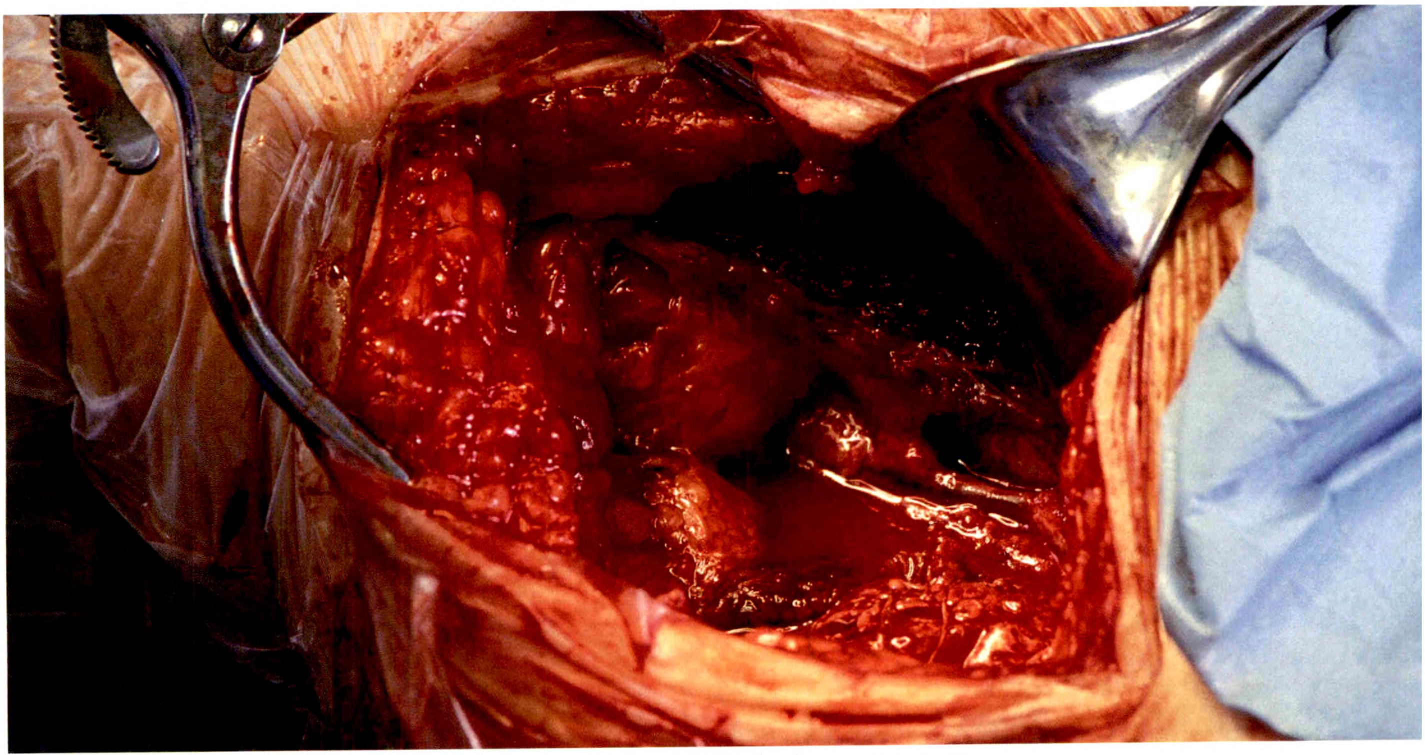

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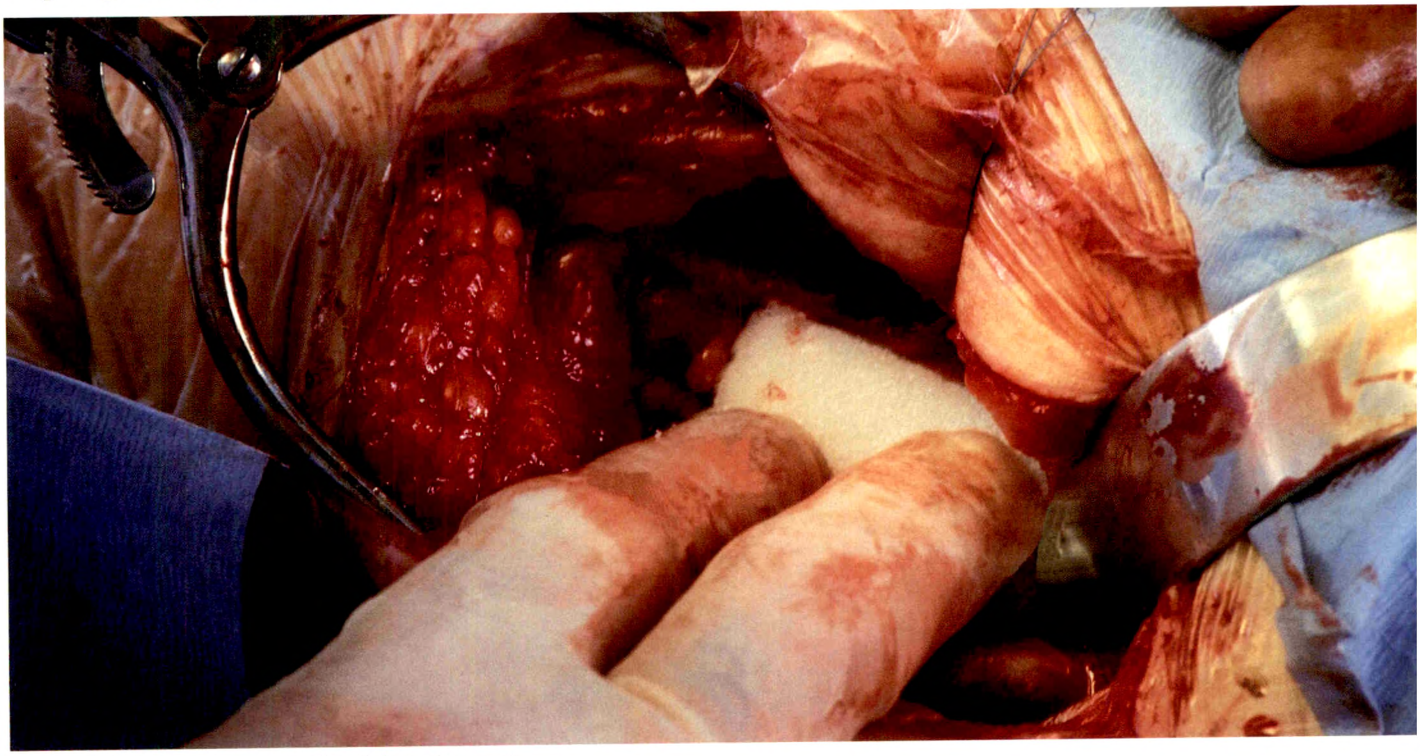

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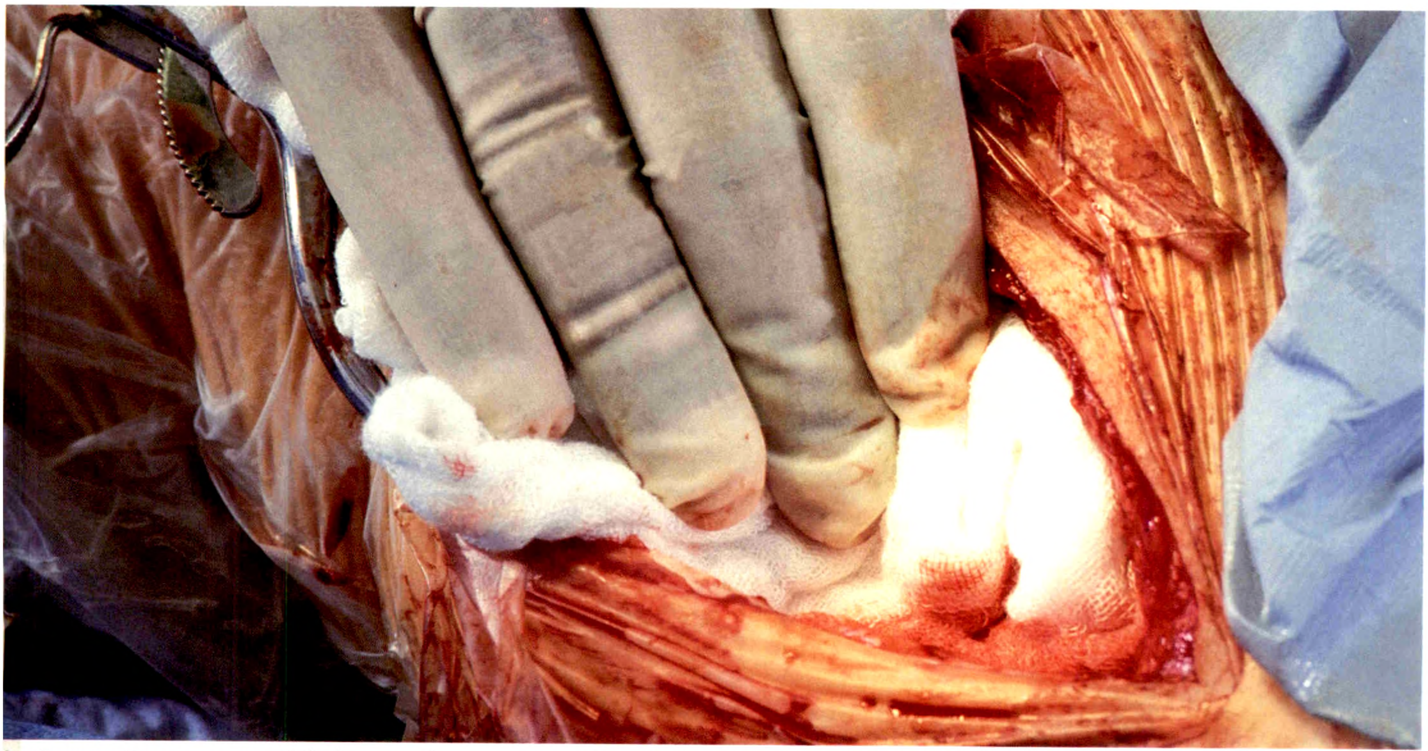

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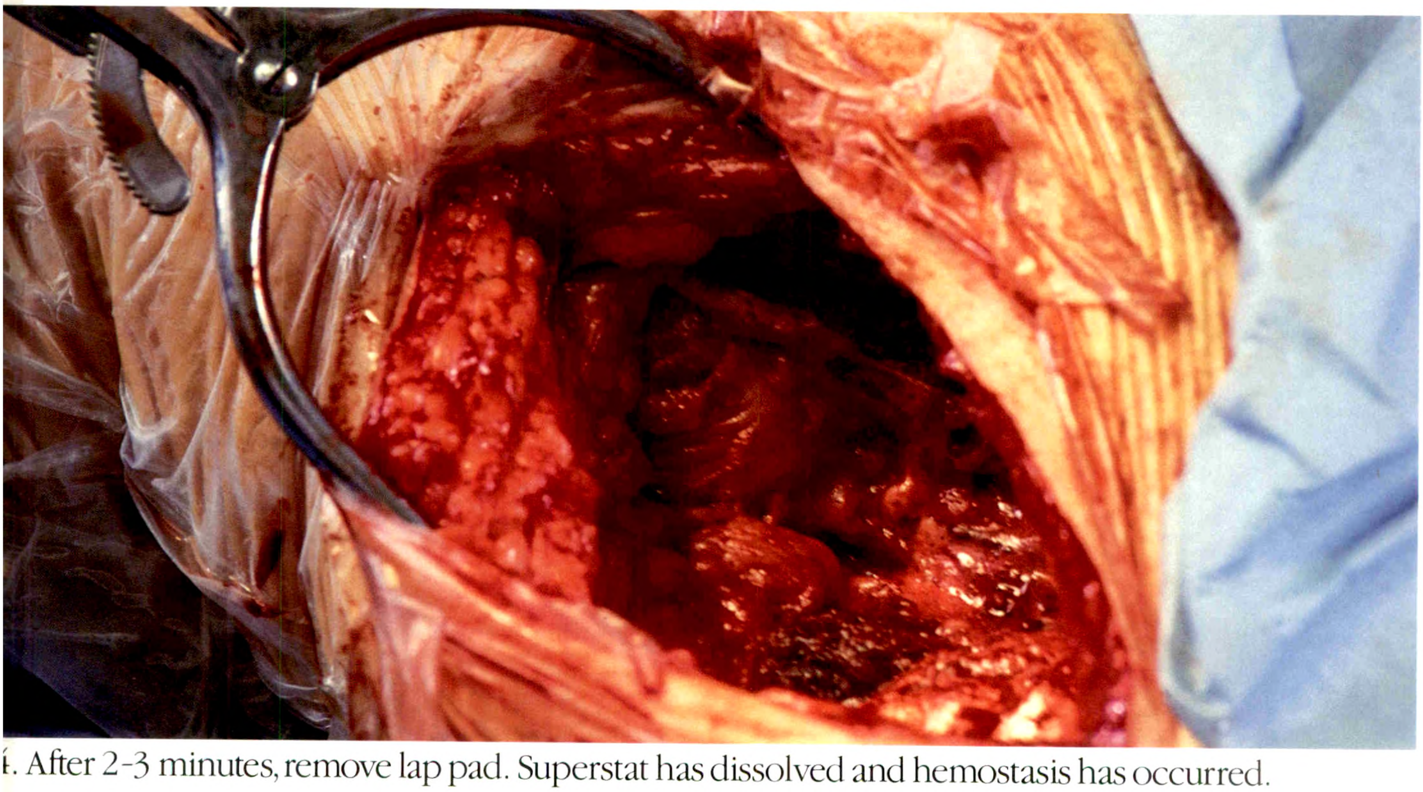

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Controversial Aspects of Coronary Endarterectomy

C. Minale, MD, S. Nikol, MD, M. Zander, MD, R. Uebis, MD, S. Effert, MD, and
B. J. Messmer, MD

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Between 1980 and 1987, 635 patients underwent coronary bypass grafting combined with coronary endarterectomy. A total of 728 vessels were endarterectomized and grafted. There were 15 early deaths (2.3%). The mortality rate was higher (7.8%) for multiple-vessel endarterectomy ($p < 0.05$). The ratio of MB fraction of creatine kinase to total creatine kinase was greater than or equal to 0.10 in 48% of the cases. The first consecutive 132 survivors were followed for an average of 16 months (range, 4 months to 5 years). No late deaths occurred. Fifty-nine unselected patients underwent postoperative recatheterization at a mean interval of 18 months. An improvement in heart wall contractility could be detected in 13 patients (16.5%) and deterioration in 14 patients (17.7%). A more detailed analysis of wall contractility showed a higher rate of improvement in the posterior wall than in the anterior wall ($p > 0.05$). Furthermore, the better the contractility before operation, the greater the rate of deterioration after operation ($p < 0.05$). Despite an average of 55% of all endarterectomized vessels being occluded or severely restenosed, 90% of the patients were clinically improved. A multiparametric analysis revealed that the revascularization of myocardial areas that required endarterectomy had no significant influence with respect to clinical improvement. Endarterectomy should be limited, whenever possible, to myocardial areas with already impaired contractility. Endarterectomy of multiple branches should be treated with caution because the risk of deterioration is potentiated, with a significantly higher perioperative mortality rate.

(Ann Thorac Surg 1989;48:235–41)

Endarterectomy of the coronary arteries was introduced originally by Bailey and colleagues in 1957 [1]. In the early days this technique was applied in combination with a patch plasty in proximal lesions and was, therefore, suitable for only a small number of patients. Continued development, especially by the Cleveland Clinic [2–4] and Johnson and associates [5, 6], resulted in a new and more extended surgical approach to advanced coronary artery disease. Coronary endarterectomy now represents a well established complementary technique to coronary artery bypass grafting.

Since 1972, an increasing number of reports have been published on this subject, most of them dealing with technical aspects, operative risk factors, early and late clinical results, and patency rates of endarterectomized coronary arteries [3–11]. Nevertheless, the method remains controversial. The question has been raised as to whether or not extended endarterectomy in coronary arteries supplying myocardial areas with a high component of fibrosis is still meaningful [12]. This aspect and the question of whether or not coronary endarterectomy may be more harmful than beneficial [13] prompted us to study left ventricular wall motion in patients undergoing coronary endarterectomy.

Material and Methods

Study Patients

Between January 1980 and April 1987, 635 patients underwent coronary artery bypass grafting combined with coronary endarterectomy of one or more coronary arteries. There were 567 men and 68 women with an average age of 56 ± 4 years (range, 37 to 75 years). Indication for operation was angina in 419 patients (66%) and angina combined with signs of cardiac failure in 216 patients (34%). According to the Canadian Cardiovascular Society classification [14], 63 patients (10%) were in class II, 546 patients (86%) were in class III, and 26 patients (4%) were in class IV. Serious dysfunction of the left ventricle with a left ventricular end-diastolic pressure of 20 mm Hg was present in 111 patients (17.5%). Altogether, 728 vessels were treated by endarterectomy. This represents 30% of the 2,390 grafted vessels in this group of patients (Table 1). Indication for endarterectomy included complete coronary occlusion, local intimal ulceration, and diffuse severe calcification with serial stenoses.

Surgical Technique

Operation was performed using cardiopulmonary bypass and moderate hypothermia of 28°C. Cardiac arrest was achieved with cold crystalloid cardioplegic solution. The left ventricle was vented in all patients. Distal anastomoses were accomplished during cardiac arrest, whereas aortic anastomoses were performed during reperfusion and the rewarming period. Endarterectomy was done manually, with the aid of either a dissector or a Mosquito clamp. On the right coronary artery and occasionally on the distal left anterior descending coronary artery (LAD),

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Table 1. Frequency of Endarterectomy Performed on the Different Coronary Artery Branches

Variable	No.	%
Total CABG	2,390	
Total endarterectomy	728	30.0
Artery		
LAD	167	23.0
DG	45	6.0
Cx	75	11.0
RCA	441	60.0
Number of vessels		
One	563	88.7
Two	51	8.0
Three or more	21	3.3

CABG = coronary artery bypass grafting; Cx = circumflex artery; DG = diagonal branch; LAD = left anterior descending coronary artery; RCA = right coronary artery.

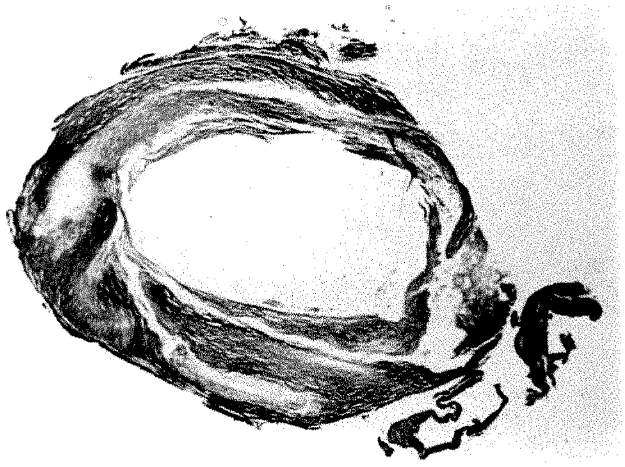

Fig 2. Histological cross-section of an endarterectomy core. Severe intimal fibrotic and atheromatous islands are evident. (Elastica Van Gieson's stain; ×16 before 25% reduction.)

dissection was started at the site of the arteriotomy and carried out distally as far as possible by the half-closed technique. At the LAD, a long incision of the vessel was preferred (Fig 1) to reopen important septal and diagonal branches and because better control of the completeness of the endarterectomy is achieved under direct vision. Histological specimens of the removed core are shown in Figures 2 to 4.

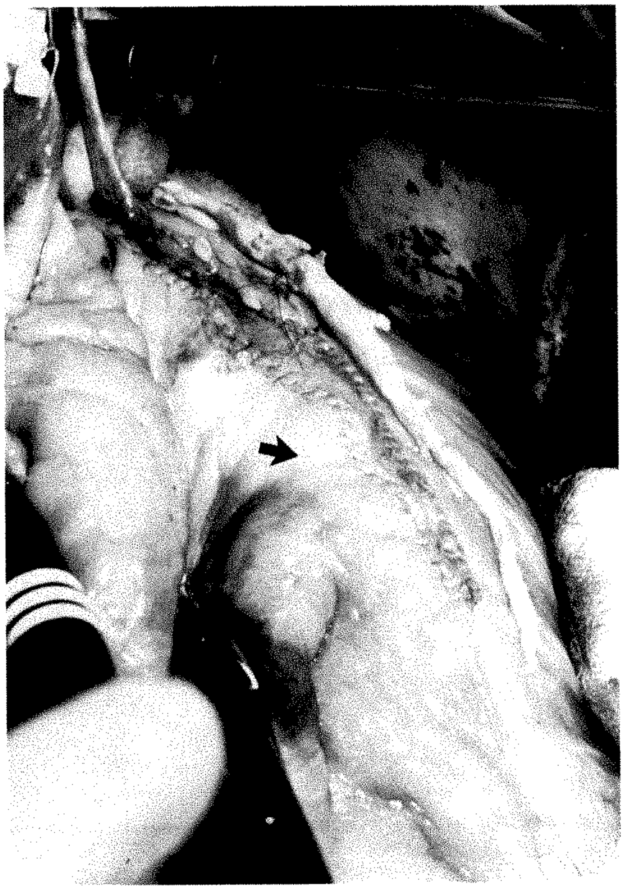

Fig 1. Vein graft (arrow) *anastomosed over a long incision of the left anterior descending coronary artery. The endarterectomized core is demonstrated on the right of the vein path.*

Postoperative Treatment and Control

Anticoagulation with heparin hydrochloride was started six hours postoperatively and continued until dicoumarine, generally given after the second postoperative day, was fully effective. In addition, aspirin (500 mg/day) was administered intravenously for 2 days. In the long term, patients were kept on dicoumarine for six months, combined with a low dose of aspirin (100 mg/day), which was subsequently continued.

Levels of creatine kinase (CK) and its myocardial-specific isoenzyme CK-MB were measured and the complete electrocardiogram was recorded six hours after the operation, as well as on the first, second, and fifth postoperative day. After discharge from the hospital, patients underwent a check-up at regular intervals. A

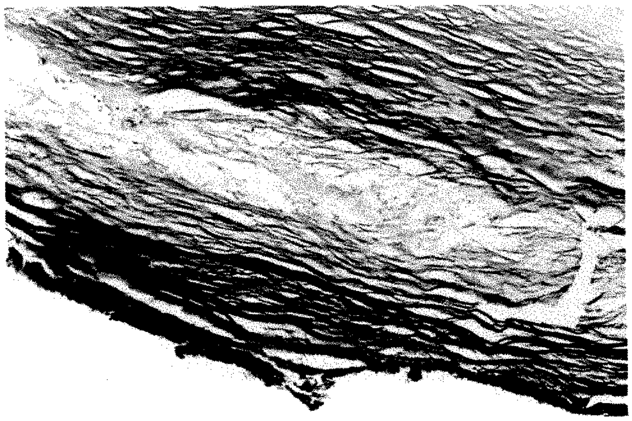

Fig 3. Magnification of an atheromatous plaque from Figure 2 containing cholesterol crystals. (Elastica Van Gieson's stain; ×250 before 35% reduction.)

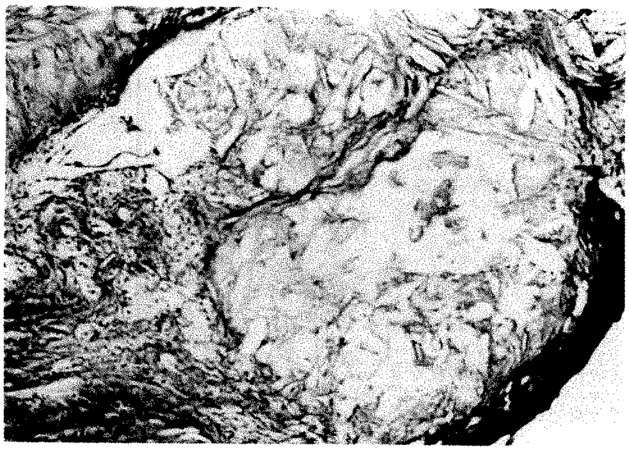

Fig 4. Greater magnification of the cholesterol plaque in Figure 3. To the left of the plaque there is an inflammatory response to the thrombus with beginning organization. (Elastica Van Gieson's stain; ×400 before 35% reduction.)

series of 59 nonselected patients underwent recatheterization study between 2 weeks and 4 years (average, 18 ± 13 months) after the operation. In these patients, preoperative and postoperative left ventricular angiograms were scored according to the criteria shown in Table 2. Nonobstructed patency of vein grafts was considered a prerequisite for evaluating the corresponding myocardial area.

Statistics

Continuous variables are presented as the mean ± 1 standard deviation (SD) from the mean. Proportion and percentage differences were tested against the null hypothesis by means of the Pearson χ^2 test. Continuous variable differences among different groups and within the single groups were tested against the null hypothesis by means of the unpaired and paired Student's t test, respectively.

Results

There were 15 early deaths, resulting in a hospital mortality of 2.3%. Eight patients died because of documented myocardial infarction and 6 because of primary myocardial failure. One patient died from multiorgan failure after iatrogenic injury of the liver. Independent risk factors influencing mortality were multiple-vessel endarterectomy and impaired left ventricular function (Table 3). Hospital morbidity included severe arrhythmia (sinoatrial and atrioventricular block, multifocal premature beats, and ventricular flutter and fibrillation) in 156 patients (25%), low cardiac output in 35 patients (5.6%), and clinically evident but nonfatal myocardial infarction in 12 patients (2%).

Table 2. Scoring System

Score	Left Ventricle Wall	Coronary Vessels
1	Normal	Normal
2	Hypokinetic	Stenotic
3	Akinetic	Occluded
4	Dyskinetic	. . .

Table 3. Risk Factors for Hospital Mortality

Factor	No.	%	p Value
Artery			>0.05
LAD	5	3.0	
Cx	2	2.7	
RCA	12	2.7	
Number of vessels			<0.01
One vessel	11	2.0	
Two vessels	4	7.8	
LVEDP			<0.001
≤20 mm Hg	10	1.9	
>20 mm Hg	5	4.5	

Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; LVEDP = left ventricular end-diastolic pressure; RCA = right coronary artery.

As shown in Table 4, peak CK levels averaged 336 U (range, 33 to 2,214 U). The peak of the CK-MB isoenzyme ranged from 2 to 300 U (mean, 30 U). Although the average ratio between CK-MB and CK was 0.08 and, therefore, below the critical value of 0.1, it exceeded this limit in 48% of the patients, indicating a higher incidence of perioperative myocardial damage than was clinically evident.

Perioperative or early postoperative low cardiac output had to be treated with the intraaortic balloon pump in 57 patients (8.9%). The mortality in this subgroup was 19.2% (11 patients), which was significantly higher ($p < 0.00001$) than in the remaining 578 patients, in whom four deaths accounted for a mortality of 0.7%.

Follow-up study of the first consecutive 132 survivors averaged 16 ± 9.7 months (range, 4 to 68 months), adding up to a total of 177 patient-years. When last subjected to a check-up, 59 (46%) were in functional class I or II, 67 (52%) were in class III, and 3 (2%) were in class IV compared with 11%, 86%, and 3%, respectively, before operation. Even though 54% of the patients are still in functional class III and IV, the improvement for the whole group is highly significant (Table 5).

Of the 59 patients who were reinvestigated angiograph-

Table 4. Creatine Kinase and CK-MB Isoenzyme Pathway

	n	Mean Value	Range
CK (IU/L)	175	336 ± 219	33–2,214
CK-MB (IU/L)	138	30 ± 22	2–300
CK-MB/CK	138[a]	0.08 ± 0.04	0.01–0.20

[a] The ratio of MB isoenzyme to creatine kinase was >0.10 in 48% of patients studied.

CK = creatine kinase; CK-MB = myocardial-specific isoenzyme of creatine kinase.

Table 5. Results of Follow-up Study of 132 Survivors of Endarterectomy

	Preoperative					
	All Patients		Survivors Followed Up		Postoperative (Survivors Followed Up)	
NYHA	No.	%	No.	%	No.	%
I, II	63	10	14	11	59	46
III	546	86	111	86	67	52
IV	26	4	4	3	3	2
Total	635		129		129[a,b]	

[a] $p < 0.0001$ versus all patients preoperatively; [b] $p < 0.0001$ versus preoperative class of survivors followed up.

NYHA = New York Heart Association.

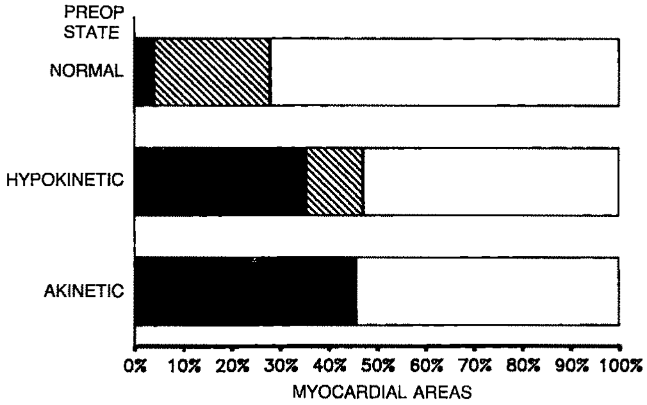

*Fig 5. Modifications of myocardial contractility after coronary artery endarterectomy with respect to the preoperative myocardial state. Preoperative contractile state of myocardium is reported on the ordinate. Postoperative modifications of myocardial contractility are illustrated in bars (*solid = *improved;* hatched = *worsened;* open = *unmodified). Proportions are based on the number of examined myocardial areas after endarterectomy of the corresponding coronary arteries.*

ically, 20 had endarterectomy of the LAD or a dominant diagonal branch, or both, whereas the remaining 39 had endarterectomy of the right coronary or circumflex artery, or both. The classification of these two groups assumes that the anterior wall and apex were perfused through the LAD and a diagonal branch, and the posterolateral wall through the right coronary and circumflex artery branches.

Preoperative and postoperative left ventricular wall motion scores and left ventricular end-diastolic pressure values are shown in Table 6. The average local wall motion score changed by 0.05, 0.31, and −0.06 for the anterior wall, the apex, and the posterior wall, respectively (Table 6). Before operation, the anterior wall showed significantly better contractility than the posterior wall ($p = 0.015$). After operation, contractility of the anterior wall and the apex deteriorated, whereas posterior wall motion improved slightly. Specifically, 13 myocardial areas (16.5%) showed an improvement after endarterectomy, 14 (17.7%) were worse, and 52 (65.8%) were unchanged. However, none of these changes was significant.

In preoperatively normal-contracting areas, a deterioration was observed in 24%. In originally hypokinetic or akinetic areas, local wall motion improved in 35.3% and 45.5%, respectively (Fig 5). A detailed analysis of regional wall motion changes is given in Figure 6. Compared with the preoperative values, left ventricular end-diastolic pressure did not change significantly (Table 6).

In regard to early (12 hours) postoperative enzyme levels, the CK-MB/CK ratio was greater than 0.10 in 20 (45%) of 44 patients with unmodified or worsened local wall motion, but only in 4 (36%) of 11 with improved contractility ($p > 0.05$).

At angiographic control study after a mean follow-up period of 18 ± 13 months (range, 0.5 to 48 months), 45% of all endarterectomized coronary arteries were patent. The patency rate for vessels of the left coronary system

Table 6. Modifications of Heart Wall Contractility and Left Ventricular End-Diastolic Pressure After Coronary Endarterectomy

Variable	n	Preoperative[a]	Postoperative[a]	Average Change	p Value
AW[b]	20	1.20 ± 0.41	1.25 ± 0.44	0.05	0.60
Ap[b]	20	1.62 ± 0.87	1.93 ± 1.07	0.31	0.15
PW[b]	39	1.71 ± 0.83	1.65 ± 0.75	−0.06	0.65
LVEDP	53	14.21 ± 6.34	12.92 ± 5.15	−1.29	0.15

[a] Data are reported as mean ± standard deviation; [b] Measured on a scale of 1 through 4; see Table 2.

Ap = apex; AW = anterior wall; LVEDP = left ventricular end-diastolic pressure (mm Hg); PW = posterior wall.

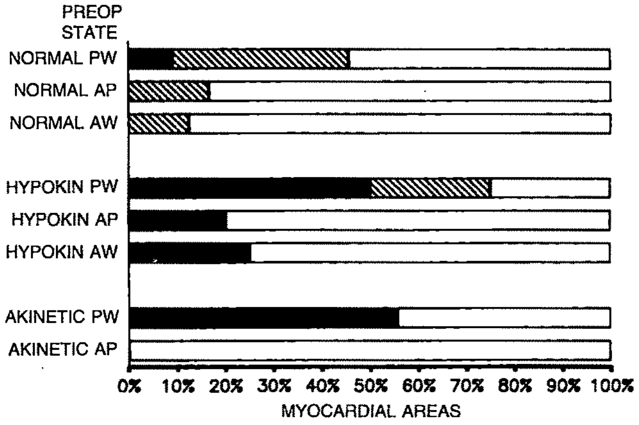

*Fig 6. Modifications of regional myocardial contractility after coronary artery endarterectomy with respect to the preoperative myocardial state. The regional contractile state of myocardium before operation is reported on the ordinate. The postoperative modifications of myocardial contractility are illustrated in bars (*solid = *improved;* hatched = *worsened;* open = *unmodified). Proportions are based on the number of examined myocardial areas after endarterectomy of the corresponding coronary arteries. (AP = anteroposterior;* AW = *anterior wall;* HYPOKIN = *hypokinetic;* PW = *posterior wall.)*

Table 7. Patency Rates of Grafted Vessels[a]

	With Endarterectomy		Without Endarterctomy		
Artery	No.	%	No.	%	p Value
LAD	4/18	22.2	28/33	84.9	<0.001
DG	1/3	33.3	11/17	64.7	>0.05
Cx	2/3	66.7	29/42	69.0	>0.05
RCA	20/36	55.6	8/11	72.7	>0.05
Total	27/60	45.0	76/103	73.8	<0.001

[a] Mean follow-up time = 18 ± 13 months.

Cx = circumflex coronary artery; DG = diagonal branch; LAD = left anterior descending coronary artery; RCA = right coronary artery.

was 29.2% compared with 55.6% for the right coronary artery system ($p < 0.05$). Without thromboendarterectomy, the patency rate was 73.9% for the left coronary system and 72.7% for the right coronary artery system. The most significant difference was found for the LAD, in which the patency rate after endarterectomy was only 22.2%, compared with 84.9% when no endarterectomy was performed ($p < 0.001$) (Table 7). Altogether a significantly lower patency rate was observed for endarterectomized vessels (45%) than for grafted coronary arteries without endarterectomy (73.8%) (Table 7). The vessel score was improved only for the left circumflex and right coronary arteries ($p < 0.05$) (Table 8).

Clinically, 53 endarterectomized and angiographically controlled patients have showed improvement since operation, 2 had no change, and 4 were worse than before the operation. However, 90% of the patients (Table 9) still had complaints independent of the patency state of the endarterectomized and grafted vessel ($p > 0.05$). In the subset of patients with endarterectomy of an anterior wall vessel, dyspnea was present in 92% of patients with an occluded vessel compared with 50% of patients with a patent vessel ($p < 0.01$).

Comment

Coronary endarterectomy has been controversial since it was first applied by Bailey and colleagues [1] in 1957. Because of the fear of side branch obstruction by the so-called snow-plug phenomenon [8] it had been abandoned, but it was reintroduced shortly after introduction of coronary bypass grafting (when for a certain period gas endarterectomy had been propagated). The vast experience with coronary artery bypass grafting and the gratifying results led to the expansion of the indication for surgical therapy, including more and more patients with diffuse coronary disease [1–4, 7, 15]. Furthermore, as a result of advances in angioplasty techniques, patients who are referred to the surgeon commonly tend to have more extensive coronary heart disease. It is, therefore, not surprising that coronary endarterectomy should experience a revival, not because the perplexities on its value have been dissipated, but because there is no alternative. In many patients, bypass grafting alone cannot achieve optimal reperfusion, and additional endarterectomy may be imperative.

Table 8. Modifications of Coronary Artery State After Endarterectomy

Artery	n	Preoperative[a]	Postoperative[a]	Average Change	p Value
LAD[b]	20	2.25 ± 0.44	2.17 ± 0.85	−0.08	0.75
DG[b]	19	2.00 ± 0.33	2.05 ± 0.71	0.05	0.75
Cx[b]	39	2.04 ± 0.57	1.47 ± 0.67	−0.57	0.0001
RCA[b]	39	2.40 ± 0.61	1.76 ± 0.77	−0.64	0.0001

[a] Data are reported as mean ± standard deviation; [b] Scored from 1 through 3; see Table 2.

Cx = circumflex branches; DG = diagonal branch; LAD = left anterior descending coronary artery; RCA = right coronary artery.

Table 9. Influence of Coronary Endarterectomy on Symptoms

	Patent Grafts		Occluded Grafts		
Symptoms	No.	%	No.	%	p Value
Angina	22/29	75.9	28/31	90.3	>0.05
Dyspnea	15/25	60.0	21/28	75.0	>0.05
Angina and/or dyspnea	25/28	89.0	31/32	97.0	>0.05

Initially, endarterectomy of the right coronary artery system was preferred because of its technical simplicity and the relatively low risk. Expansion to the left coronary artery system has been mainly propagated by Bernowitz and associates [10, 11] and adopted by others [7, 15–17]. Although endarterectomy of the left coronary artery and especially of the LAD was supposed to present a higher operative risk, this could not be confirmed by the present data, with mortality rates of 3% for the LAD, 2.7% for the circumflex artery, and 2.7% for the right coronary artery (Table 3). Multiple vessel endarterectomy and impaired left ventricular function, however, proved to be significant risk factors. This is in full accordance with recently published data by Brenowitz and associates [11], who reported a mortality rate of 4.8% for the isolated right coronary endarterectomy and 7.9% for the left coronary endarterectomy, but also a significant difference between patients with single-vessel and multiple-vessel endarterectomy.

At late postoperative study, 46% of the patients in the present series were in New York Heart Association functional class I or II, and 90% noted an improvement after the operation. Symptoms, however, persisted proportionally to some extent in patients with either patent or occluded endarterectomized coronary arteries (Table 9). These results indicate a negative selection bias of patients in whom scar tissue, despite reperfusion, remains scar tissue, rather than of a lack of skill. Patency rates of endarterectomized vessels were significantly lower than those of nonendarterectomized vessels (45% versus 73%). The Milwaukee group [11] reported a patency rate of 71.1% after endarterectomy. Whether these differences

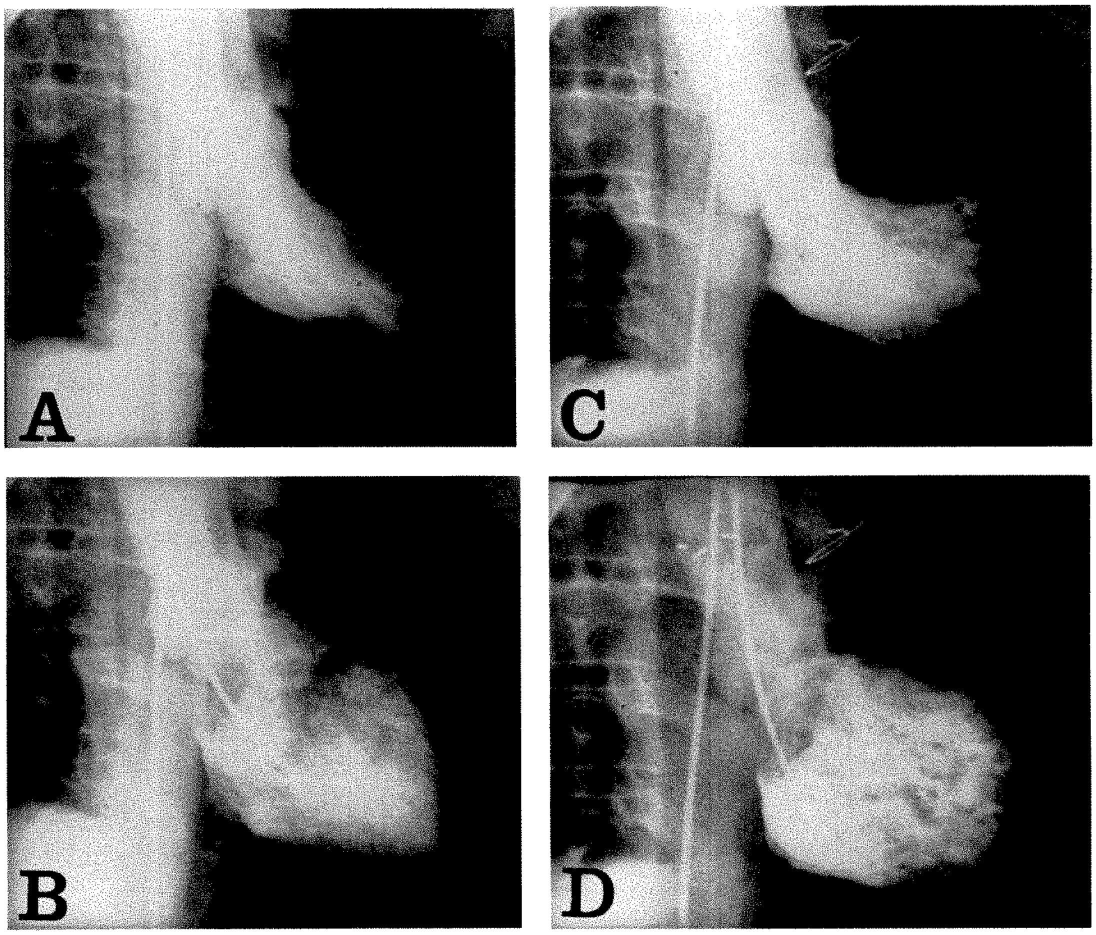

Fig 7. Ventriculography of a patient who underwent endarterectomy and coronary artery bypass grafting of the left anterior descending coronary artery: (A) preoperative end-systolic phase; (B) preoperative end-diastolic phase; (C) postoperative end-systolic phase; (D) postoperative end-diastolic phase. Despite patency of the bypass graft and the left anterior descending coronary artery after endarterectomy, (C) reveals an appreciable deterioration of myocardial contractility with respect to the preoperative state shown in (A).

are due to our preferred technique of anterograde and retrograde closed endarterectomy of the right coronary artery and the frequently performed semiclosed extrusion of the cylinder between two incisions on the LAD is difficult to determine. The fact is that an extensive open endarterectomy is a time-consuming procedure that sometimes results in a higher operative mortality rate.

The hospital mortality rate in the present series of patients is significantly higher than that in another series of our patients in which no endarterectomy was done (2.3% versus 1.7%, 35 deaths in 1,965 patients; $p < 0.001$) (unpublished data), but compares favorably with that in a larger series of patients in which extensive endarterectomy was done on a routine basis [11].

More important than graft and vessel patency is regional wall motion within the perfusion area of an endarterectomized coronary artery. A comparison of preoperative and late postoperative regional wall motion showed no change in two-thirds of the studied areas, whereas improvement and deterioration were equal. Parallel to the low patency rate of the grafts to an endarterectomized vessel was the amelioration of contractility within the pertinent myocardial area. In the present series, endarterectomy of the LAD had a lower rate of myocardial improvement than endarterectomy of the right coronary artery (Fig 6). In addition, the risk of deterioration is even higher in patients with preoperatively well-contracting myocardium (Fig 7) than in patients with already impaired ventricular function. This latter observation reflects the high rate of perioperative subclinical myocardial infarction noted in the present series (Table 4). Deterioration of left ventricular function after endarterectomy of coronary arteries has also been observed by other investigators [16], who noted an average change in global ejection fraction from 55.2% ± 10.7% preoperatively to 48% ± 15% postoperatively.

The fact that in formerly normally contracting myocardial areas further improvement cannot be expected and that in formerly hypokinetic or akinetic areas higher rates of improvement rather than deterioration in wall motion can be obtained postoperatively indicates the benefit of endarterectomy primarily in the latter category of patients. In vessels perfusing normally contracting areas, endarterectomy should be performed cautiously. Even in the event of the relevant vessel's being completely destroyed even though the myocardium is still functioning well, it might be better to improve only the collateral flow rather than to force anterograde perfusion. These rules are even more important if global left ventricular function is poor. In such cases, the operative risk is high [11] and those myocardial areas that still function well should, whenever possible, be protected from additional damage. In the present series, the risk of the operation was increased even more by the practice of multiple endarterectomy. The higher frequency of subclinical myocardial infarction after endarterectomy explains why the operative risk increases significantly with the number of vessels that are endarterectomized.

In conclusion, endarterectomy of coronary vessels should be considered as an adjunctive procedure to coronary artery bypass graft grafting when the patient's condition is extremely critical. It should be applied preferentially to the posterior wall with impaired myocardial contractility. Coronary endarterectomy should never be considered as a convenient alternative to making more anastomoses to distal disease-free branches. In the case of walls that contract well, even in the presence of obstructed vessels, endarterectomy should be, whenever possible, avoided. Collateral perfusion should be enhanced through simple bypass grafts to vessels supplying adjacent myocardial areas. The only exception to these rules exists in cases of unsuspected ulceration, thrombosis, or severe calcification of an artery that has been opened to perform an anastomosis. In such cases, if a more distal anastomosis to a disease-free section of the artery is not possible, a limited local endarterectomy should be attempted instead.

We are aware that in the event of severe diffuse peripheral occlusion of the coronary arteries, if a surgical approach is chosen, there is no other alternative than endarterectomy. However, considering the operative risk and the limited long-term benefit in terms of myocardial contractility and survival even in larger series of patients [11], it would perhaps be more reasonable to continue to treat these critically ill patients conservatively. For select patients, among those who are not responsive to medical treatment, heart transplantation may be an acceptable option.

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Evaluation of Prostacyclin Analogue OP-41483 as an Adjunct to Crystalloid Cardioplegia in Infants and Children

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A chemically stable prostacyclin analogue (PGI_2-A, carbacyclin, OP-41483) was evaluated as an adjunct to potassium cardioplegia in infants (n = 13) and children (n = 32), in whom the current potassium cardioplegia may be limited in its effects. PGI_2-A was added in a dose of 300 μg/L to the potassium cardioplegic solution. Postoperatively, peak levels of the myocardial-specific isoenzyme of creatine kinase (MB-CK) were compared for the PGI_2 group and a control group (n = 65). In patients 1 year of age or older (n = 32 and 49 for the PGI_2 and control groups, respectively), the MB-CK level was significantly lower in the PGI_2 group only when compared between the subgroups with an aortic cross-clamp time of 120 minutes or more (n = 9 and 10; MB-CK level, 35.2 ± 15.6 vs 68.3 ± 32.4 IU/L; $p < 0.05$). In patients less than 1 year of age, in whom aortic cross-clamp times were generally less than 120 minutes, the MB-CK level was also lower in the PGI_2-A group than in the control group (n = 13 and 16; MB-CK level, 33.6 ± 14.3 vs 61.6 ± 36.3 IU/L; $p < 0.05$). Infants less than 6 months of age (n = 18) underwent ultrastructural assessment of left ventricular myocardial biopsy specimens, and the PGI_2-A group showed better results in mitochondrial and intracellular edema scores. This clinical trial showed beneficial effects of PGI_2-A used with crystalloid potassium cardioplegia in infants and children.

(Ann Thorac Surg 1989;48:242–6)

Prostacyclin (PGI_2) is a prostanoid produced by the endothelial cells of the blood vessels [1] and has been known to have beneficial effects in attenuating myocardial injuries caused by ischemic insult [2–6]. As the mechanism involved, a cytoprotective effect and antiplatelet and vasodilating actions have been postulated. In extracorporeal circulation, PGI_2 has been used to modulate platelet activation, which may compromise postoperative hemostasis [7, 8]. However, PGI_2 is highly unstable and also has a strong vasodilating action, precluding use in patients. Recently, chemically stable analogues have become available and have been investigated in experimental myocardial ischemia and heart preservation [6, 9–11]. Our previous experimental study with a PGI_2 analogue has shown its myocardial protective effect when used as an adjunct to potassium cardioplegia crystalloid [12]. Aherne and associates [13] have also studied PGI_2 in an experimental setting. However, no attempts have been reported in patients. We selected infants and children, in whom the current methcd seems limited in its effects [14, 15], for the evaluation of PGI_2 analogue.

Material and Methods

Of 110 infants and children less than 13 years of age who underwent open heart operation at Osaka University Hospital during 1985 to 1987, 45 patients were assigned in a random fashion to receive the PGI_2 analogue OP-41483 (PGI_2-A) as an adjunct to potassium cardioplegia. The PGI_2 group consisted of 13 infants less than 1 year of age (including 2 neonates) and 32 children aged 1 to 13 years. The control group consisted of 16 infants (including 3 neonates) and 49 children. The patients had various cardiac anomalies, which are shown by group in Table 1. Patients who died within 24 hours after operation during the same time period were excluded from the study (n = 5, all with PGI_2).

Method of Myocardial Protection

CARDIOPLEGIC SOLUTION. The basic cardioplegic solution used in all patients was high-potassium cardioplegic solution with insulin and glucose. The composition of the solution is shown in Table 2. The original solution of high osmolarity (solution 1) was used in the first 87 patients, and the remaining 23 patients received a lower osmolarity solution with added calcium (solution 2). No significant difference was found in the distribution of these two types of cardioplegic solutions used in the groups with or without PGI_2-A, either in the whole group or in subgroups separated by age and aortic cross-clamp time. The percentage of patients who received solution 2 in each

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Table 1. Cardiac Lesions in Patients Studied

Cardiac Lesions	PGI_2[a]	Control[a]
Ventricular septal defect	8 (2)	22 (10)
Atrial septal defect	3 (1)	4 (0)
Pulmonary stenosis	1 (1)	4 (1)
Tetralogy of Fallot	9 (0)	10 (0)
Pseudotruncus arteriosus	3 (1)	7 (1)
Endocardial cushion defect	3 (2)	3 (1)
Transposition of the great arteries	3 (2)	2 (1)
Truncus arteriosus	3 (3)	1 (1)
Double-outlet right ventricle	2 (0)	2 (0)
Single ventricle	8 (0)	5 (0)
Miscellaneous	1 (0)	5 (1)
Total	45 (13)	65 (16)

[a] Numbers in parentheses indicate number of patients aged less than 1 year.

group ranged from 21.6% to 30.0%. The initial dose of cardioplegic solution was 10 mL/kg body weight, followed by a half dose every 30 minutes. In infants and neonates, a single-dose method with the same initial dose was used. Topical cooling with iced slush was used, and myocardial temperature was maintained at less than 15°C.

PROSTACYCLIN ANALOGUE. OP-41483 is a chemically stable derivative of carbacyclin (15-cyclopentanyl-ω-pentanor-5(e)-carbacyclin; Ono Pharmaceutical Company, Osaka, Japan). This analogue was delivered in the form of a dry powder in an ampule; it was dissolved in distilled water before use. In a rat heart perfusion model ($n = 3$), coronary flow after cardioplegic arrest was measured to obtain a dose–response curve for PGI_2-A added to cardioplegia solution 2. The percent recovery of coronary flow at 60 minutes of reperfusion after 20 minutes of global warm ischemia with the use of potassium cardioplegia containing different doses of OP-41483 was examined. The doses used were 150, 300, 450, and 600 μg/L. The recovery curve of coronary flow was almost flat above 300 μg/L (Fig 1), and this dose was used for the following study.

Table 2. Composition of Cardioplegic Solutions

Solution	1	2
Glucose (g/L)	60	55
Insulin (U/L)	12	11
Potassium (mEq/L)	18	18
Calcium (mM/L)	. . .	1.2
Magnesium (mM/L)	. . .	16
pH	7.8	7.8
Osmolarity (mosm/L)	380	375
PGI_2 (μg/L)	(300)	(300)

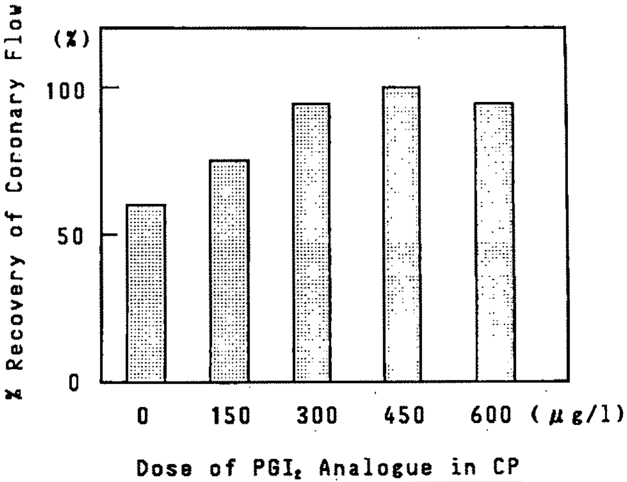

Fig 1. Dose–response relationship of PGI_2 analogue OP-41483 to the myocardial blood flow recovery after cardioplegic arrest using isolated rat heart perfusion model ($n = 3$). (CP = potassium cardioplegia.)

MYOCARDIAL PROTECTIVE EFFECT. The myocardial protective effect was assessed by peak serum creatine kinase isoenzyme (MB-CK) release during the first 24 postoperative hours in the following two groups: children over 1 year of age, and infants less than 1 year of age. In addition, the children's group was divided into two subgroups according to the aortic cross-clamp time divided by 120 minutes.

For those patients less than 6 months of age, myocardial biopsy findings were compared. The average age was 1.7 ± 1.9 months in the PGI_2A group ($n = 9$) and 2.6 ± 2.4 months in the control group (not significant [NS]). The average aortic cross-clamp time was 77 ± 21 minutes in the PGI_2 group and 75 ± 26 minutes in the control group (NS). Myocardial biopsy specimens were taken from the left ventricular apex just before aortic cross-clamping and about 15 minutes after removal of the cross-clamp. Ultrastructural assessment was made in terms of mitochondrial change and intracellular edema. The mitochondrial damage was assessed by scoring from grade 0 (no damage) to grade 4 (severe irreversible damage) in 300 mitochondria, and the average score was obtained in each patient [15]. The intracellular edema was also assessed by a similar scoring method.

Statistical analysis was made using the two-tailed Student's t test for unpaired samples, and paired t test for paired samples. Before Student's t test, the F distribution was analyzed for each of the compared samples, and the Welch t test was used when the variance was different. Statistical significance was indicated when the p value was less than 0.05. Data are shown as mean ± the standard deviation of the mean.

Results

There were no significant differences in age and aortic cross-clamp time between the two groups as a whole or between the subgroups separated by age (1 year) and aortic cross-clamp time (120 minutes) (Tables 3–5).

Table 3. Comparison Between PGI_2 and Control Groups for Overall Groups and Subgroups Divided by Aortic Cross-clamp Time[a]

Variable	PGI_2 Group	Control Group
Overall Group		
n	45	65
Age (yr)	3.5 ± 3.8	3.9 ± 3.9
AXC (min)	95.2 ± 45.0	84.8 ± 51.8
MB-CK (U/L)	33.5 ± 15.0	35.3 ± 28.9
AXC < 120 min		
n	35	53
Age (yr)	3.1 ± 3.6	2.8 ± 3.0
AXC (min)	77.4 ± 2.78	65.3 ± 28.9
MB-CK (U/L)	33.1 ± 15.3	38.2 ± 31.4
AXC > 120 min		
n	10	12
Age (yr)	5.9 ± 4.4	6.4 ± 4.7
AXC (min)	157.6 ± 37.7	165.8 ± 51.3
MB-CK (U/L)	34.9 ± 14.8[b]	60.9 ± 31.4[b]

[a] Where applicable, data are given as mean ± standard deviation. [b] $p < 0.05$ for PGI_2 group versus control group.

AXC = aortic cross-clamp; MB-CK = myocardial-specific isoenzyme of creatine kinase.

Peak MB-CK value

There was no significant difference in peak MB-CK level between the overall groups with and without PGI_2 (Table 3). In the subgroups with an aortic cross-clamp time less than 120 minutes (n = 88), there was also no significant difference in peak MB-CK level between the two groups. In those with an aortic cross-clamp time greater than 120 minutes, however, the PGI_2 group had significantly lower values compared with the control group.

Table 4. Comparison Between PGI_2 and Control Groups for a Subgroup of Patients Aged More Than 1 Year[a]

Variable	PGI_2 Group	Control Group
Overall		
n	32	49
Age (yr)	4.8 ± 3.8	5.0 ± 3.8
AXC (min)	101.3 ± 48.2	88.3 ± 53.5
MB-CK (U/L)	33.4 ± 15.7	36.1 ± 28.7
AXC < 120 min		
n	23	39
Age (yr)	4.1 ± 3.5	4.4 ± 3.4
AXC (min)	78.5 ± 27.8	68.5 ± 30.3
MB-CK (U/L)	32.7 ± 15.8	28.4 ± 22.3
AXC > 120 min		
n	9	10
Age (yr)	6.6 ± 4.1	6.7 ± 4.2
AXC (min)	159.8 ± 39.3	165.3 ± 55.6
MB-CK (U/L)	35.2 ± 15.6[b]	68.3 ± 32.4[b]

[a] Where applicable data are given as mean ± standard deviation. [b] $p < 0.05$ for PGI_2 group versus control group.

AXC = aortic cross-clamp; MB-CK = myocardial-specific isoenzyme of creatine kinase.

Table 5. Comparison Between PGI_2 Group and Control Group for a Subgroup of Patients Aged Less Than 1 Year[a]

Variable	PGI_2 Group	Control Group
n	13	16
Age (mo)	4.9 ± 3.1	4.9 ± 3.8
AXC (min)	80.1 ± 32.7	74.4 ± 46.0
MB-CK (U/L)	36.6 ± 14.3[b]	61.6 ± 36.3[b]

[a] Where applicable, data are given as mean ± standard deviation. [b] $p < 0.05$ for PGI_2 group versus control group.

AXC = aortic cross-clamp; MB-CK = myocardial-specific isoenzyme of creatine kinase.

In patients over 1 year of age, there was no significant difference in peak MB-CK value between the two groups (Table 4). In the subgroup of those with an aortic cross-clamp time less than 120 minutes, there was also no significant difference between the PGI_2 group and the control group, but for those with an aortic cross-clamp time of more than 120 minutes, peak MB-CK level was significantly lower in the PGI_2 group compared with the control group.

In patients less than 1 year of age, there was a significantly lower peak MB-CK value in the PGI_2 group compared with the control group (Table 5). No separate comparison was made by aortic cross-clamp time because of the limiting number of patients.

Ultrastructural Assessments

Ultrastructural assessments were performed on patients aged less than 6 months.

MITOCHONDRIAL SCORE. The average mitochondrial score before aortic cross-clamping was 0.3 ± 0.2 in the control group and 0.4 ± 0.4 in the PGI_2 group; there was no

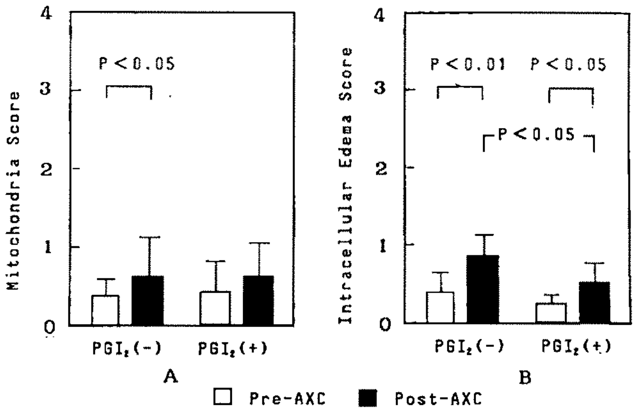

Fig 2. Comparisons of the mitochondrial score (A) and intracellular edema score (B) for the left ventricular myocardial biopsy specimens of patients less than 6 months of age who received cardioplegia with and without PGI_2-A. (AXC = aortic cross-clamping.)

significant difference (Fig 2A). The control group showed a significant increase to 0.7 ± 0.5 after aortic cross-clamping ($p < 0.05$), whereas the PGI_2 group showed no significant increase (0.7 ± 0.4). There was no significant difference between the two groups in the values after cross-clamping.

INTRACELLULAR EDEMA SCORE. The average edema score before aortic cross-clamping was 0.2 ± 0.1 in the PGI_2 group and 0.3 ± 0.3 in the control group (NS) (Fig 2B). Both groups showed significant score increases after cross-clamping, to 0.5 ± 0.3 for the PGI_2 group and 0.9 ± 0.3 for the control group ($p < 0.05$). The score after cross-clamping was significantly lower in the PGI_2 group ($p < 0.05$).

Comment

Previous experimental studies including our own have shown the beneficial effects of PGI_2 or its analogue on the preservation of ischemic myocardium [2–4, 9–13]. Its cytoprotective effect against ischemia has been postulated as resulting from its stabilizing effect on lysosomal membranes in addition to its antiplatelet and vasodilating effects [11]. Protection of the myocardial sympathetic nerve along with the preservation of myocardial catecholamine levels have also been described for PGI_2 [16]. From this background, the myocardial protective effect of PGI_2 has been studied in experimental myocardial infarction and heart preservation. However, the assessment in cardioplegic solution has not been attempted except in experimental studies, including our own previous reports [12–14]. A clinical application has been described by Mueller and associates [17] in patients with acute myocardial infarction.

Regarding the mechanisms of this analogue in myocardial protection, its protective effects on myocardial cells and vasculature during ischemia may be direct actions of PGI_2-A. Although we have not measured the blood level of PGI_2-A in the perfusate of the cardiopulmonary circuit during reperfusion, a part of the given analogue might be returned to the cardiopulmonary bypass perfusate and have a chance to work during reperfusion by possible vasodilating and antiplatelet actions. Our experimental study showed beneficial effects of this analogue when used during reperfusion alone. These effects were comparable with those obtained with its use as an adjunct to potassium cardioplegia. These were also associated with the finding that PGI_2-A cardioplegia enhanced the endogenous PGI_2 production during reperfusion [12]. Considering that there may be associated platelet deposition to the myocardial vasculature [18], and also thromboxane production during reperfusion after global ischemia even with use of potassium cardioplegia [19], reperfusion with an increased level of endogenous PGI_2 or the presence of exogenous PGI_2 may attenuate the adverse effects related to platelet activation and vasoconstriction. As the other mechanism of myocardial protection provided by PGI_2, the vasodilating effect may also be involved in this situation by improving myocardial oxygen consumption [13].

This clinical study confirmed the beneficial effect of OP-41483 as an adjunct to potassium cardioplegia in infants and children in terms of postoperative MB-CK release and ultrastructural assessment of myocardial biopsy specimens. The methods used in this study for the assessment of the myocardial protective effect, particularly MB-CK release, may not be perfect; however, the results obtained may be enough data to evaluate the efficacy in this clinical study with various types of operation in a group of patients with congenital heart disease. The beneficial effects were obtained in patients under 1 year of age, regardless of the aortic cross-clamp time, and also in children when cross-clamp time exceeded 120 minutes. Therefore, as previously shown in our ultrastructural assessments of intraoperative myocardial biopsy specimens [15], these subgroups of infants and children are likely to sustain myocardial injuries during cardioplegia, and appear to benefit from PGI_2 cardioplegia.

This clinical trial of PGI_2 analogue indicated its beneficial effect as an adjunct to potassium cardioplegia in infants and children. The mechanism of its myocardial protection may relate to its cytoprotective as well as antiplatelet effects, but was not elucidated in this study.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 3, 1991. The closing date for registration is August 1, 1990.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

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Mediastinal Lymph Node Necrosis: A Newly Recognized Complication of Mediastinoscopy

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Eight cases of partial mediastinal lymph node necrosis identified at thoracotomy two to 17 days after cervical mediastinoscopy are described. In 6 cases, the involved nodes were grossly abnormal at operation, requiring frozen section interpretation. In the first 2 patients, the areas of nodal infarction were misinterpreted as necrotic tumor. Permanent sections from all 8 patients showed no evidence of tumor in the infarcted nodes. Factors predisposing to nodal infarction included right-sided tumor, central tumor, and large mediastinoscopic biopsy specimens. In all instances, the infarcted nodes were subcarinal and/or main bronchial. In 2 patients, left recurrent laryngeal nerve palsy occurred after mediastinoscopy. Necrosis in distal nodal areas should be recognized as a complication of thorough mediastinoscopic sampling, presumably due to interruption of arteries supplying these nodes. Awareness of this phenomenon by surgeons and pathologists may avert falsely positive gross or microscopic diagnoses of metastatic malignancy at thoracotomy.

(Ann Thorac Surg 1989;48:247–50)

Lymph node necrosis may occur during the course of various infections; as a component of hyperplasia; as a result of vascular compromise from vasculitis, occlusion, or trauma; as a benign idiopathic phenomenon; or as a reflection of malignancy [1, 2]. In cases in which some other cause is not clinically or pathologically obvious, and particularly in cases of partial nodal necrosis, malignancy is the major diagnostic consideration [2]. Malignant neoplasms associated with nodal necrosis include both lymphomas and metastatic carcinomas [1, 2].

Mediastinoscopy is a minor surgical procedure in which mediastinal lymph nodes are biopsied to assess whether or not a patient with lung cancer is a candidate for resection and possible cure [3, 4]. Patients whose nodes are found to be tumor-free, whose metastatic survey is negative for malignancy, and who are otherwise medically fit then undergo thoracotomy.

This report describes 8 patients in whom partial mediastinal lymph node necrosis occurred as a result of mediastinoscopic biopsy, causing difficulty in surgical and frozen section interpretation of the nodes at subsequent thoracotomy.

Patients and Methods

During the calendar years of 1986 and 1987, 141 patients underwent cervical mediastinoscopy followed by thoracotomy for lung carcinoma at the Vancouver General Hospital. Eight patients were found to have mediastinal lymph node necrosis at thoracotomy, and these 8 patients are described here. One of us (B.N.) was the surgeon for both procedures for all but 1 patient, and one of us (R.R.M.) examined all of the pathological specimens.

Mediastinoscopic nodal biopsies were designated by site according to the guidelines of the American Thoracic Society [5]. Two patients had sampling from location 2, 7 patients had bilateral sampling from location 4, 3 patients had bilateral sampling from location 10, 7 patients had sampling from ipsilateral location 10, and all patients had sampling from ipsilateral locations 4 and 7. The nodal samples were processed in the usual way for histological examination of hematoxylin and eosin-stained sections of paraffin-embedded tissue.

Thoracotomy was undertaken only after permanent sections of mediastinal nodes had been found to be tumor-free. The interval between mediastinoscopy and thoracotomy was 2 to 17 days (Table 1). At the time of thoracotomy, a frozen section of nodal tissue was requested if the tissue was grossly abnormal. The tumors were classified as central if involvement of a lobar or segmental bronchus could be demonstrated.

Histological grading of the characteristics of nodal necrosis was subjectively assessed on a scale of 0 through 4. Variables considered included the presence of minimally organized hemorrhage and fibrin, granulation tissue, vascular thrombi, and liquefactive versus coagulative necrosis, as previously defined [2]. Briefly, liquefactive necrosis is characterized by polymorphonuclear leukocyte infiltrate, karyorrhectic debris, and architectural obliteration, whereas coagulative necrosis is characterized by eosinophilic cell ghosts, preservation of nodal reticulin, and granulation tissue at the edge of the necrosis in healing lesions.

Results

There was no evidence of nodal necrosis or metastatic tumor in nodal tissue obtained at mediastinoscopy in any

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Table 1. Case Details

	Patient No.							
Variable	1	2	3	4	5	6	7	8
Med sample size (cm)								
Ipsilateral 10	ND	0.4	1.0	1.5	2.0	1.0	0.8	1.3
Ipsilateral 7	0.9	1.7	0.3	2.0	1.5	0.7	0.8	1.4
Resection								
Grossly abnormal lymph nodes[a]	Y	Y	N	Y	Y	N	Y	Y
Lobes	RPN	RML, RLL	RUL, RML	LPN	RML, RLL	RML, RLL	RPN	RPN
Central vs peripheral	C	C	P	C	C	C	P	C
Node histology[b]								
Hemorrhage/fibrin	4	1	1	3	2	2	4	2
Coagulative necrosis	1	2	2	3	2	1	0	1
Liquefactive necrosis	1	0	0	0	1	3	2	3
Granulation tissue	1	1	2	1	2	0	0	3
Vascular thrombi	Y	Y	Y	N	N	N	N	N
Med to resection delay (days)	2	12	2	17	2	7	7	5

[a] Abnormal lymph nodes requiring intraoperative frozen section interpretation. [b] Node histology was graded subjectively from 0 through 4.

C = central; LPN = left pneumonectomy; Med = mediastinoscopy; N = no; ND = not done; P = peripheral; RLL = right lower lobectomy; RML = right middle lobectomy; RPN = right pneumonectomy; RUL = right upper lobectomy; Y = yes.

of the patients. However, in the 8 patients reported here, partial nodal necrosis was found at thoracotomy. In 3 patients (patients 1 to 3) nodal necrosis was focal, involving only a small part of nodal cortex. In the other 5 patients, more than half of the node was necrotic, with sparing of variable relative amounts of cortex and medulla. In 3 patients, subcarinal nodes were involved, and in 1, ipsilateral main bronchial nodes were necrotic; in 4 patients, both of these nodal locations were involved. The nodes of locations 2 and 4 were not sampled at thoracotomy and, thus, necrosis in these sites could not be histologically assessed.

Further details of the 8 cases are shown in Table 1. In each case, mediastinoscopic sampling from locations 7 and 10 had been extensive. The submitted nodal biopsy specimens from one or both of these locations measured 1 cm or more in 6 of 8 patients, the other 2 patients yielding 0.8-cm and 0.9-cm lymph nodes.

Patients 4 and 8 developed left recurrent laryngeal nerve injury after mediastinoscopy. In both patients, full functional recovery occurred within 6 months to 1 year after the procedure.

At thoracotomy, 6 patients had grossly abnormal swollen and friable nodes that required frozen section interpretation. In the initial 2 patients (patients 1 and 8), before the nature of the necrosis was clear, the frozen sections were erroneously interpreted as positive for necrotic malignancy. In both patients, planned right middle and lower bilobectomy was extended to right pneumonectomy.

An unusually high proportion of tumors (6 of 8 cases) were central lesions of lobar or segmental bronchi, and all 6 had associated obstructive pneumonitis and reactive lymphadenopathy.

Histologically, all patients showed a mixed pattern of reaction (Table 1). All had partial nodal necrosis with a relatively sharp interface between necrotic and viable areas (Fig 1). Liquefactive necrosis with neutrophil reaction and karyorrhexis was seen in 5 patients. Coagulative necrosis with cell ghosts was seen in 7 patients. Granulation tissue that mimicked glandular structures was seen in 6 patients. Vascular thrombi could be identified in only 3 patients. Metastatic malignancy was not found in any of the nodal locations containing necrotic tissue.

There was no correlation between histological details of the necrosis and time interval between mediastinoscopy and thoracotomy. Specifically, hemorrhage and fibrin with little organization did not correlate with a short interval, and well-developed granulation tissue was not necessarily indicative of a long interval. Coagulative necrosis was not restricted to patients with observable vascular thrombi. Coagulative and liquefactive necrosis coexisted in 4 patients.

Comment

The classification of lymph node necrosis is based on a combination of pattern of necrosis and, if known, cause [2]. *Total* nodal necrosis may be related to sepsis, malignancy [1, 2], trauma, or vascular obstruction. Some cases defy etiological explanation [6] yet follow a benign course. *Partial* nodal necrosis is usually due to malignancy, granulomatous inflammation, or a florid hyperplastic reaction to various infections or idiopathic immune challenges. Metastatic carcinoma is a major differential diagnostic consideration in the absence of obvious reactive nodal morphology. A single case of partial axillary nodal infarction after fine needle aspiration biopsy has been described

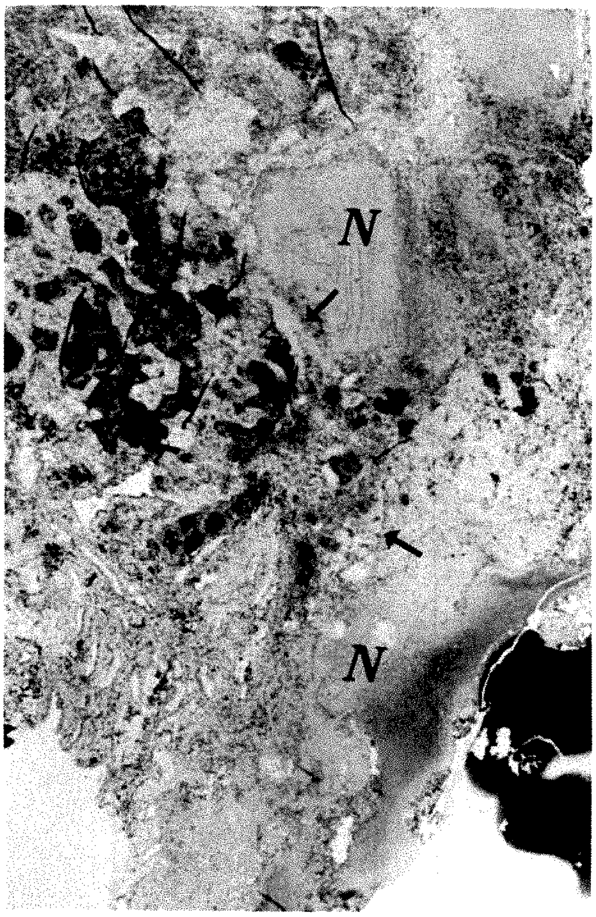

Fig 1. Partial nodal necrosis with sharp demarcation (arrows) *between necrotic* (N) *and viable areas (hematoxylin and eosin, ×2.5).*

[7]. Lymph node infarction due to recent operation has been described [2], but is rarely recognized in practice. A partial explanation for this is that there are few instances when operative nodal biopsy precedes by several days resection of a primary tumor and examination of its regional nodes. The practice of mediastinoscopy followed by thoracotomy is a notable exception to this rule.

The anatomy of the bronchial arteries supplying these nodes renders them vulnerable to injury at mediastinoscopy. The bronchial arteries usually arise from the aorta or from intercostal arteries and follow a variable course [8]. Most frequently, the left bronchial artery arises from the aorta and almost immediately branches into a vascular network to supply the left main bronchus, location 7 and 10L nodal sites. It follows that injury to the left bronchial artery by cervical mediastinoscopy would be unlikely. The right bronchial artery usually arises from intercostal arteries [9]; it forms end arteries for the right hilar soft tissues and supplies most of the location 4R, 7R, and 10R and some of the location 4L and 10L mediastinal nodal tissue. The more tortuous course of the right bronchial artery may place it at higher risk for injury, as reflected by ischemia to the subcarinal and right hilar tissues. This was suggested in our series, in which 7 of the 8 cases involved right distal nodal stations. The absence of nodal tumor in permanent sections in any of these patients reinforces the interpretation of surgical trauma rather than malignancy as the cause of the observed necrosis.

Several factors were typically seen in cases in which nodal necrosis was identified. In all instances, extensive nodal biopsy samples of the main bronchial/subcarinal stations had been taken. Six of the eight resections contained central tumors with obstructive pneumonitis and reactive lymphoid hyperplasia. One could speculate that these two factors predisposed to arterial interruption and partial nodal necrosis, respectively. Four of the resections were bilobectomies and four were pneumonectomies. The hilar dissection required to do these procedures may have increased the likelihood of seeing the abnormal tissue at thoracotomy. Alternatively, the correlation between extended resection and identification of nodal infarction may be related to central tumor location. Overall, the incidence of identifying postmediastinoscopy nodal necrosis apparently depends on the size of mediastinal biopsy samples, the size of mediastinal nodes, the side and site of primary tumor, and perhaps additional factors.

The overall complication rate of mediastinoscopy is 1% to 3%, the most common complications being hemorrhage, pneumothorax, tracheal injury, wound infection, and vocal cord paralysis [4, 10]. Although left recurrent nerve palsy may theoretically occur as a consequence of direct injury, it is difficult to accept this explanation for the 2 patients in this series who experienced this complication. No nerve segments were seen in their biopsy specimens. Electrocautery was never used in the 4L position for hemostasis to avoid heat coagulation injury to the nerve. In both patients, spontaneous recovery of function occurred, implying that the course of the nerve trunk had not been interrupted. We speculate that bronchial artery injury may be the cause of localized ischemia to the recurrent laryngeal nerve as well as mediastinal lymph node necrosis.

Lymph node necrosis has not been previously described as a complication of mediastinoscopy as far as we know. Awareness of the phenomenon of postmediastinoscopy nodal necrosis may avert a false surgical impression of the extent of disease and a false pathological impression of metastatic carcinoma.

We acknowledge Dr Kenneth G. Evans, Thoracic Surgery, Vancouver General Hospital, who was the surgeon for patient 3, and Dr Nestor L. Muller, Department of Radiology, Vancouver General Hospital, for helpful comments on the manuscript.

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REVIEW OF RECENT BOOKS

Decision Making in Surgery of the Chest
Edited by Laurens R. Pickard
Philadelphia: W.B. Saunders, 1988
168 pages, illustrated. $75.00

Reviewed by Richard M. Peters, MD

This book is taking the original decision-making type of decision tree algorithm as developed by Dr Ben Eiseman and providing it for decision-making in cardiothoracic surgery. The authorship of this book is multiple. It represents some of the leaders in general thoracic and cardiac surgery. Dr Pickard has assembled the group of authors and has obviously done a very careful job in editing the decision algorithms; the result is a very useful and quite excellent text. Obviously in such a text one will get the strong opinion of individuals, but the text is organized so that the decision algorithms are diagrams on the right side of each page and on the left side are text explanations and, equally important, references backing up the decision trees.

The diagrams provide a good review of the logic of decision-making in each of the areas. If the logic diagram is followed and the reader has any question about why the logic was chosen, he or she can refer to the text to get the reasoning behind the logic and also to refresh things that have been forgotten. The references then give the source for further review and updating. This type of presentation just waits to be put on a CD ROM or even a disk to be called up in computer systems for display and could be in part animated.

The medical knowledge being developed in these logic diagrams will, I feel sure, be available on the wards for house staff and students in the future. This is a book that all thoracic surgeons would want to have in their office for updating, and certainly it would be excellent for general surgeons and cardiothoracic residents both for clinical care and for reviewing for examinations. Dr Pickard is to be congratulated on getting this group together and organizing this book so consistently.

San Diego, California

Effect of Left Ventricular Septal Myectomy on Concurrent Mitral Regurgitation

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To assess the impact of left ventricular septal myectomy (Morrow procedure) performed for obstructive hypertrophic subaortic stenosis on co-existing mitral regurgitation, we examined the preoperative and postoperative left ventriculograms of 35 patients (13 of them women) who underwent left ventricular septal myectomy alone or with concomitant operation. The mean age was 45 ± 3 years (range, 19 to 74 years). Patients underwent left ventriculography at an average of 15 ± 3 months postoperatively (range, 1 to 78 months). Severity of mitral regurgitation was evaluated by two teams of reviewers. Mitral regurgitation due to catheter entrapment or to premature ventricular contraction or other arrhythmia was excluded. Overall, 51% of patients showed improvement in the severity of mitral regurgitation, and all those with more severe mitral regurgitation (ie, 3+) demonstrated improvement. The population was subdivided for analysis into those with coronary artery disease requiring bypass grafting at the time of left ventricular septal myectomy (n = 7, 20%) and those without coronary artery bypass grafting. Among the 7 patients undergoing bypass grafting, 71% demonstrated improvement in the degree of mitral regurgitation as compared with only 46% of those without bypass grafting ($p < 0.005$ by χ^2 analysis). Significant reductions in peak gradients at rest and in response to provocation, and in New York Heart Association functional class, also occurred in both groups.

(Ann Thorac Surg 1989;48:251–6)

The mechanism of dynamic obstruction to left ventricular outflow in patients with idiopathic hypertrophic subaortic stenosis (IHSS) involves anterior displacement of the anterior and/or posterior leaflet of the mitral valve due to Venturi effects of high-velocity blood flow through a narrowed outflow tract. Because this results in distortion of normal mitral valve coaptation, and commonly results in mitral regurgitation of variable severity in patients with obstruction, it is a reasonable assumption that operative relief of obstruction and systolic anterior motion of the valve leaflets would alleviate or abolish mitral regurgitation. This study was undertaken to investigate the impact of left ventricular myotomy and myectomy (Morrow procedure, LVMM) on mitral regurgitation in our population of patients undergoing LVMM.

Material and Methods

Population

A retrospective review of all patients undergoing LVMM as devised by Dr Andrew G. Morrow at the National Institutes of Health [1] was performed. Since August 1958, 482 patients have undergone LVMM. Of this total, 93 patients had left ventriculography both before and after operation. The preoperative and postoperative cineangiograms in 49 patients (53%) studied since August 1971 were available for review. Of these, the 35 patients (13 women) whose preoperative and postoperative left ventriculograms were of adequate quality (ie, free of atrial or ventricular arrhythmia or catheter interference with mitral valve closure) to comment on the degree of mitral insufficiency present, if any, are the basis of this report. The mean age was 45 ± 3 years (range, 19 to 74 years) at the time of operation.

Patients had a left heart catheterization and left ventriculography at an average of 15 ± 3 months postoperatively (range, 1 to 78 months). The degree of mitral regurgitation was evaluated in all cineangiograms independently by two teams of reviewers, one consisting of a cardiologist and cardiac surgical fellow, the second consisting of two cardiologists. Preoperative and postoperative films were scored according to the following scale [2]: 1+ (mild), regurgitation that essentially clears with each beat and never opacifies the entire left atrium; 2+ (moderate), regurgitation that does not clear with one beat and generally opacifies the entire left atrium faintly after several beats, although the opacification of the left atrium does not equal that of the left ventricle; 3+ (moderately severe), regurgitation completely opacifies the left atrium equal to that of the left ventricle; 4+ (severe), opacification of the entire left atrium occurs within one beat, the opacification becomes progressively more dense with each beat, and contrast medium can be seen refluxing into the pulmonary veins during left ventricular systole. The independent evaluations were in complete agreement in 47 of 70 films (67%), differed by one grade in 22 (31%, 14 preoperatively, 8 postoperatively), and differed by two grades in one postoperative film. After independent evaluation, a

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Table 1. Operative Procedures

LVMM	25
LVMM + pacemaker	2
LVMM + CABG	7[a]
LVMM + aortic valvulotomy	1

[a] One patient also underwent pacemaker implantation.

CABG = coronary artery bypass grafting; LVMM = left ventricular myotomy and myectomy.

consensus was reached with respect to the adequacy of a given film to allow determination of the presence of mitral regurgitation and, if present, the degree of regurgitation.

Preoperative and postoperative left ventricular outflow gradients at rest and in response to provocation with the Valsalva maneuver, amyl nitrite, and isoproterenol, and New York Heart Association functional class, were also recorded and compared.

Operations

The indications for LVMM for all patients have been continued symptoms despite maximal medical therapy and resuscitation after sudden death. The objective of operative intervention is maximal relief of resting and provokable left ventricular outflow tract gradients with minimal morbidity and low operative mortality. Since mid-1983 cold crystalloid cardioplegia has been used for myocardial protection rather than a brief period of 30°C ischemic arrest followed by coronary artery perfusion. Intraoperative echocardiography to accurately determine septal thickness and morphology has also been used since 1983. The operative procedures performed included 27 isolated LVMMs, and LVMM with concomitant procedure other than pacemaker implantation in 8 patients (23%) (Table 1). Among the patients undergoing concomitant coronary artery bypass grafting (CABG), 4 received single saphenous vein grafts to the right coronary artery, 1 received vein grafts to the left anterior descending and right coronary artery, and 2 received single obtuse marginal vein grafts.

Statistical Analysis

Comparisons of mean values were carried out using Student's paired *t* test. Significance was considered to occur at the 0.05 level. One-way analysis of variance and correlation coefficients were calculated using standard computational formulas. All data are expressed as mean ± the standard error of the mean.

Results

Hemodynamics

Overall, significant reduction occurred in the average peak left ventricular outflow tract gradient at rest and in response to provocation (Table 2). Four patients (11%)

Table 2. Preoperative and Postoperative Angiographic, Hemodynamic, and Functional Data[a]

Variable	n	Preoperative	Postoperative	Improvement (%)	*p* Value
Overall group					
Resting gradient (mm Hg)	35	61 ± 8	14 ± 4	78	$p < 0.0005$
Gradient with provocation (mm Hg)					
Valsalva maneuver	20	86 ± 9	30 ± 7	66	$p < 0.0005$
Amyl nitrite	17	85 ± 6	28 ± 6	67	$p < 0.0005$
Isoproterenol	15	117 ± 8	48 ± 10	59	$p < 0.0005$
LVMM without coronary artery bypass grafting					
Severity of mitral regurgitation (0–4+)	28	1.3 ± 0.2[b]	0.8 ± 0.2	38	$p < 0.05$
Resting gradient (mm Hg)	28	68 ± 9[b]	17 ± 5	75	$p < 0.0005$
Gradient with provocation (mm Hg)					
Valsalva maneuver	15	93 ± 8	31 ± 9	67	$p < 0.0005$
Amyl nitrite	13	83 ± 5	31 ± 8	63	$p < 0.0005$
Isoproterenol	13	123 ± 8	52 ± 11	58	$p < 0.0005$
Functional class (1–4)	28	3.1 ± 0.1	2.2 ± 0.2	29	$p < 0.0005$
LVMM with coronary artery bypass grafting					
Severity of mitral regurgitation (0–4+)	7	1.6 ± 0.4	0.6 ± 0.2	63	$p < 0.025$
Resting gradient (mm Hg)	7	35 ± 13	2 ± 1	94	$p < 0.025$
Gradient with provocation (mm Hg)					
Valsalva maneuver	5	66 ± 24	12 ± 6	82	$p < 0.05$
Amyl nitrite	4	93 ± 19	19 ± 5	80	$p < 0.005$
Isoproterenol	2	80 ± 5	19 ± 7	76	$p < 0.01$
Functional class (1–4)	7	3.3 ± 0.3	2.3 ± 0.4	30	$p < 0.05$

[a] All data are paired and expressed as means ± standard errors. [b] Not significantly different from value with bypass grafting by one-way analysis of variance.

LVMM = left ventricular myotomy and myectomy.

Table 3. Effect of Left Ventricular Myotomy and Myectomy on Angiographic Demonstration of Mitral Regurgitation

		Postoperative[a]		
Group	Preoperative	MR Improved or Abolished	MR Unchanged	MR Worsened or Acquired
Overall (n = 35)				
MR present	25	18 (72)	5 (20)	2 (8)
MR absent	10	. . .	6 (60)	4 (40)
LVMM without CABG (n = 28)				
MR present	19	13 (68)	4 (21)	2 (11)
MR absent	9	. . .	6 (67)	3 (33)
LVMM with CABG (n = 7)				
MR present	6	5 (83)	1 (17)	. . .
MR absent	1	. . .	. . .	1 (100)

[a] Numbers in parentheses are percentages of preoperative total.

CABG = coronary artery bypass grafting; LVMM = left ventricular myotomy and myectomy; MR = mitral regurgitation.

had no resting gradient preoperatively, whereas 17 (49%) had none postoperatively (χ^2, $p < 0.005$).

The population was subdivided for analysis into those with coronary artery disease requiring CABG at the time of LVMM (n = 7) and those without CABG (n = 28) to determine if a differential response to operation could be discerned. Reduction to clinically insignificant values occurred in the average peak left ventricular outflow tract gradients in both groups (Table 2). In 1 patient not undergoing concomitant CABG, the postoperative resting gradient remained greater than 100 mm Hg, despite the fact that the patient was in functional class I and was much improved. The degree of mitral regurgitation improved from 3+ to 2+, which may in part explain the patient's symptomatic and functional improvement. Significant reductions in the average of peak gradients also occurred in response to provocation with the Valsalva maneuver, amyl nitrite, and isoproterenol in both groups.

Angiography

Of the overall group (n = 35), 25 patients (71%) had mitral regurgitation preoperatively. Of these, 13 had no evidence of regurgitation postoperatively, and an additional 5 had improvement in severity. Eleven patients (31%) were without change and 6 (17%) had worsening of mitral regurgitation. One patient undergoing CABG acquired 1+ mitral regurgitation postoperatively, and 3 patients without CABG acquired mitral regurgitation (1+ in 1 patient and 2+ in 2 patients) (Table 3). All patients with severe mitral regurgitation (ie, 3+; no patient had 4+) improved postoperatively.

Among the 7 patients undergoing concomitant CABG, of whom 6 had mitral regurgitation, 71% (n = 5) demonstrated improvement in the degree of mitral insufficiency; 1 (14%) was unaffected and 1 (14%) showed deterioration (Table 3). The incidence of mitral regurgitation decreased from 86% (n = 6) preoperatively to 57% (n = 4) postoperatively ($p < 0.005$), with an improvement in severity of 72% among those with regurgitation preoperatively (1.8 ± 0.3 preoperatively to 0.5 ± 0.2 postoperatively, $p < 0.005$). In contrast, only 46% (n = 13) of patients without CABG had improvement in mitral regurgitation; 36% (n = 10) were unaffected and 5 (18%) had increased regurgitation (Table 3). The incidence of regurgitation in the group without CABG decreased from 68% (n = 19) preoperatively to 43% (n = 12) postoperatively ($p < 0.005$) with improvement in severity from 1.8 ± 0.2 to 0.8 ± 0.2 ($p < 0.005$) among those patients with regurgitation preoperatively. These differences in response to LVMM were highly significant ($p < 0.005$ by χ^2 analysis) for the improved and unaffected patients. Analysis of variance did not show a significant difference in the mean preoperative severity of regurgitation between groups, nor a difference in the mean preoperative resting left ventricular outflow tract gradient ($p > 0.05$) to account for this differential response (Table 2). The favorable redistribution in severity of mitral regurgitation postoperatively is shown in Figure 1.

Correlation

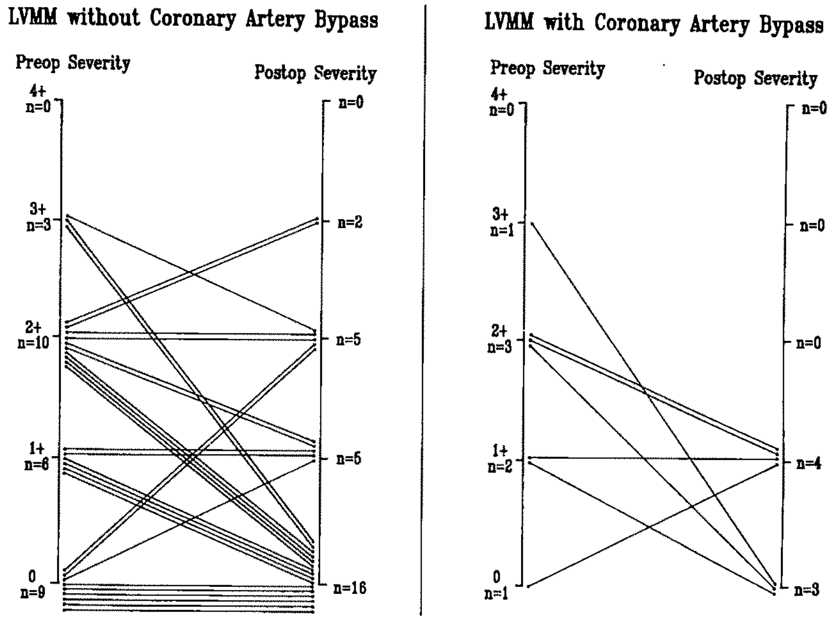
Although minimal correlation was found between severity of basal left ventricular outflow obstruction and severity of mitral regurgitation preoperatively in the overall group ($r = 0.29$) and in the group not undergoing CABG ($r = 0.29$), a marked correlation was present in the group with CABG ($r = 0.69$).

Calculation of correlation coefficients to detect a relationship between the change in severity of mitral regurgitation and hemodynamic parameters revealed some association with the reduction in resting left ventricular outflow gradient in the group without CABG ($r = 0.27$) but negligible association with the change in gradient in response to provocation with the Valsalva maneuver ($r = 0.15$), amyl nitrite ($r = 0.01$), or isoproterenol ($r = 0.04$) in the same group. In the group undergoing concomitant CABG, negligible association was found between the change in severity of mitral regurgitation and the resting outflow tract gradient ($r = 0.19$), and some association with the change in gradient in response to the Valsalva maneuver ($r = 0.41$). However, although very strong associations were found with the change in response to amyl nitrite ($r = 0.94$) and isoproterenol ($r = 1.0$), the significance of this statistical finding is suspect as these subgroups were constituted by only 4 and 2 patients, respectively.

Function

New York Heart Association functional class improved an average of 29% from a mean of 3.1 ± 0.1 preoperatively to 2.2 ± 0.2 at the time of postoperative left ventriculogram ($p < 0.0005$) in the group without CABG and from 3.3 ± 0.3 to 2.3 ± 0.4 in the group undergoing CABG ($p < 0.05$, 30%).

Fig 1. Preoperative and postoperative severity of mitral regurgitation in patients undergoing left ventricular myotomy-myectomy (LVMM) *for idiopathic hypertrophic subaortic stenosis.*



Comment

The reported incidence of associated mitral regurgitation in obstructive IHSS ranges from 40% to 100%, depending in part on whether the valvular incompetence is diagnosed angiographically, echocardiographically, or by indicator dilution studies [3–10]. Mitral incompetence was present in 71% of our patients preoperatively. Although it has generally been held that correctly performed septal myectomy usually relieves associated mitral regurgitation [11], few reports have been more than anecdotal and few have carefully excluded cases of catheter interference with mitral valve coaptation or premature ventricular contraction or other arrhythmias as confounding variables inducing mitral incompetence. Morrow [5] noted that 10 of 11 patients (91%) who had evidence of mitral regurgitation preoperatively had fully competent valves after operation. Agnew and associates [8] reported on 28 patients in whom both preoperative and postoperative cineangiograms were available for comparison. Of these, 16 had mitral regurgitation preoperatively and of these, the regurgitation was abolished in 14 (88%). A somewhat lesser effectiveness in abolition of mitral insufficiency was noted by Schmahl and colleagues [6], who reported the persistence of regurgitation postoperatively in 3 of 7 patients (43%). They noted, however, that in only 1 patient was the regurgitation clinically significant.

In comparison with these reports, 51% of our population overall showed improvement in the severity of mitral regurgitation with a further increased response in patients with coronary artery disease requiring concomitant CABG (improvement in 71% vs 46% of patients without CABG) and those with the most severe regurgitation (improvement in 100%). Our overall result may reflect the appearance at operation of a much broader spectrum of septal morphology and more symmetrical hypertrophy of the septum per se than that originally described by Braunwald and co-workers [12]. In fact, since 1983 intraoperative echocardiography has been performed in all patients being considered for LVMM. This was performed with the transducer placed directly on the heart and 2-dimensional and M-mode echocardiograms obtained in the long and short axes. If at the time of operation the ventricular septum measured less than 18 mm at the area of proposed resection, a mitral valve replacement was performed rather than LVMM. Current studies of potential high-risk patients undergoing operative intervention for IHSS, either LVMM or mitral valve replacement, will determine the short-term and long-term benefits and complications associated with each procedure.

The differential response of mitral regurgitation to LVMM in the presence or absence of coronary artery disease is not explained by a difference in degree of outflow obstruction or severity of mitral insufficiency preoperatively between groups, and may be due to ischemic papillary muscle dysfunction corrected by concomitant CABG. In addition, the greater correlation ($r = 0.69$ vs $r = 0.29$) found between severity of basal outflow obstruction and severity of mitral regurgitation preoperatively in the group with coronary artery disease may explain the improved response of mitral regurgitation to LVMM in these patients.

The precise mechanism or mechanisms responsible for mitral regurgitation in IHSS are believed to be linked to those responsible for left ventricular outflow obstruction. Although abnormal insertion of mitral valve leaflets has been reported [13], as has leaflet thickening presumably secondary to trauma [14], these cases are believed to account for a minority of cases of mitral insufficiency associated with IHSS. Systolic anterior motion of the mitral valve leaflets with early systolic apposition to the ventricular septum resulting in mechanical obstruction to left ventricular emptying is believed to be the major cause of obstructive IHSS [9, 15–18]. In fact, the degree of systolic anterior motion has been found to be proportional to the severity of left ventricular outflow obstruction [19], and its disappearance after LVMM in the majority of patients corresponds with a successful hemodynamic result with reduction of outflow tract gradients [6, 8, 13, 20, 21].

The question then concerns the mechanism by which systolic anterior motion occurs. Reis and associates [21] have shown that asymmetric septal hypertrophy results in anterior-posterior displacement of papillary muscles. During ventricular contraction this malalignment is accentuated and results in pulling of the anterior mitral leaflet toward the hypertrophied septum, which obstructs the left ventricular outflow tract during systole and causes mitral regurgitation [14]. Successful LVMM results in posterior-superior realignment of the papillary muscles and consequent relief of left ventricular outflow obstruction and associated mitral regurgitation [21].

Systolic anterior motion is also presumed secondary to a Venturi effect as a result of high-speed streaming of ejected blood through the left ventricular outflow tract [17, 19, 22, 23]. It is not surprising, therefore, that relief of left ventricular outflow obstruction with a reduction in high-velocity streaming and Venturi forces would result in a decrease in the degree of mitral regurgitation. In fact, Spirito and colleagues [22] have shown echocardiographically an increase in left ventricular outflow tract dimension postoperatively after LVMM, which would have the effect of reducing the velocity of blood flow during ejection with reduction or abolition of Venturi forces responsible for systolic anterior motion, the subaortic gradient, and mitral regurgitation. Further, Nishimura and coworkers [24] found that mitral regurgitation was related to the degree of systolic anterior motion, and that the maximal amount of mitral regurgitation on color flow imaging occurred late in systole after the appearance of turbulent flow in the left ventricular outflow tract that indicates obstruction. In addition, the peak velocity detected in the left ventricular outflow tract was positively correlated with the degree of systolic anterior motion, supporting the postulation that systolic anterior motion and mitral regurgitation are induced by a Venturi effect.

Wigle and associates [10] estimated mitral regurgitation by dye-dilution techniques and demonstrated a decrease in mitral regurgitation with pharmacological reduction of left ventricular outflow obstruction as well as an increase in mitral regurgitation with pharmacological intensification. The degree of mitral regurgitation varied directly with the severity of outflow tract obstruction in the majority of patients, and was believed to be secondary to the obstruction. Wigle and associates [10] concluded in 1969, due to the above results, in conjunction with the abolition of left ventricular outflow obstruction and mitral regurgitation in response to LVMM, that left ventricular muscular abnormality and not the anterior mitral leaflet was of primary importance in causing obstruction.

Agnew and associates [8] noted that in addition to abnormal papillary muscle orientation due to the pattern of hypertrophy, excessive chordal traction and lack of normal apex to base systolic shortening with marked circumferential contraction, as previously shown by Klein and colleagues [25], may cause or contribute to abnormal mitral valve movement and are unlikely to be directly influenced by operation. These authors postulated that once obstruction has occurred the pressure relationships between the base of the left ventricle, the outflow tract, and the left atrium cause further displacement of both mitral leaflets into the outflow tract. Whereas the anterior leaflet is able to flex into this position, the posterior leaflet is extended and stretched taut, thus losing its normal area of coaptation with the displaced anterior leaflet, allowing regurgitation to occur.

Additional factors that should be mentioned with respect to the incidence of mitral regurgitation after LVMM include global dysfunction as a result of ischemic damage or poor myocardial preservation or direct injury to the mitral valve apparatus during septal myectomy. These factors would tend to influence the incidence of regurgitation in opposite directions. In 2 patients poor left ventricular function postoperatively raised the possibility of such global insult. In 1 patient the degree of mitral regurgitation remained unchanged at 1+, and in the other it decreased from 1+ to 0. No cases of iatrogenic damage to the mitral valve were detected. Finally, despite careful adherence to strict criteria for the angiographic grading of mitral regurgitation, application of the stated criteria remains a qualitative assessment.

In conclusion, this study has demonstrated that approximately one half of all patients undergoing LVMM for palliation of obstructive IHSS may derive improvement in the severity of associated mitral regurgitation after operation. Of those improved postoperatively, over one half had complete abolition of mitral regurgitation. However, virtually all patients with more severe mitral regurgitation may demonstrate improvement (100% in this study). Although a greater response of coincident mitral regurgitation to LVMM was found in the group undergoing concomitant CABG, this could be explained by possible correction of ischemic papillary muscle dysfunction as well as an increased correlation between severity of basal left ventricular outflow tract obstruction and severity of mitral regurgitation preoperatively. It is suggested that an enhanced improvement in mitral regurgitation may be expected if such a correlation exists, even in the absence of a component of correctable ischemic coronary artery disease. Once again, this study has also demonstrated that significant hemodynamic and functional improvement may be expected after LVMM.

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Complications After Esophagogastrectomy Using Stapling Instruments

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We studied 195 patients undergoing esophageal resection using stapling instruments during a period of over 8.5 years. Of these, 178 (91.2%) underwent operation for malignant disease. Operative death occurred in 19 patients (9.7%). Nine (4.6%) postoperative complications, excluding stricture formation, were related to the use of stapling instruments, including two operative deaths (1.0%). Anastomotic leaks and gastrotomy staple line leaks were the most common complications (four each). In 7 patients (3.6%) the circular stapler tore the esophagus; anastomotic leaks subsequently developed in 43% of these patients. After we began oversewing gastrotomy staple lines in 1984, we experienced only one gastrotomy leak due to a technical error. Postoperative stricture formation occurred soon after resection and responded well to one or two dilations. It is better to err on the side of choosing too small a stapling head when performing an esophageal anastomosis because this may reduce the incidence of leaks, and further strictures are easily dealt with.

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Esophageal resection remains an important means of relieving dysphagia in patients with benign and malignant obstruction of the esophagus. Recent advances in surgical techniques and postoperative management have helped to lower the operative mortality of this procedure, but long-term survival remains illusive in patients undergoing esophageal resection for malignant disease. One manifest advance in esophageal surgery has been the introduction of stapling instruments to facilitate resection and reestablish esophageal continuity [1–4]. Although earlier reports have confirmed the safety and efficacy of these devices, large series follow-up over long time periods is lacking [5–7].

We have used stapling instruments exclusively to perform esophageal resections since 1980, when they became generally available. This study relates our experience using stapling instruments during a period of over 8 years and describes the common errors we have encountered as well as methods we have found helpful.

Material and Methods

The hospital notes of all patients referred for treatment of esophageal cancer as well as of 17 patients who underwent esophageal resection for benign esophageal strictures between January 1980 and May 1988 were analyzed retrospectively. One hundred ninety-five patients underwent resection using stapling instruments; 178 (91.2%) for malignant tumors of the middle and lower third of the esophagus, and 17 for benign reflux-induced strictures that failed to respond to dilation.

Preoperative assessment consisted of history and physical examination, barium swallow, biochemical screening, esophagoscopy, and in cases of midesophageal tumors, bronchoscopy. Ultrasound and computed tomographic scans were obtained when indicated for evaluation of local and metastatic spread that would preclude operative intervention. The presence of vocal cord paralysis, tracheoesophageal fistula, and enlarged cervical lymph nodes and the demonstration of large hepatic metastases by ultrasound scanning were accepted indications of inoperability. Patients who were considered fit enough to withstand thoracotomy underwent resection; age was not considered a contraindication to operation.

Our operative technique, which uses stapling instruments whenever possible, has been previously described [3]. If the tumor is considered resectable, the stomach is mobilized fully using the LDS stapler (U.S. Surgical Corporation, Norwalk, CT) to ligate and divide vessels along the lesser and greater curvature of the stomach. Care is taken to preserve the right gastric and gastroepiploic vessels. The left gastric artery is doubly tied and divided at its origin using the LDS stapler at its origin.

Care is taken not to mobilize the proximal esophagus more than is necessary and to keep the various staple lines well apart so as to maintain viability of the intervening stomach wall. Sizers are not used to determine the size of the end-to-end anastomotic (EEA) stapler required to reduce to a minimum the trauma caused to the proximal esophagus. All straight staple lines are oversewn.

The cartridge and anvil are examined for circular tissue fragments (donuts). Two circumferential tissue fragments incorporating all layers indicate a well-fashioned anastomosis. All straight staple lines are reinforced with a

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continuous 3-0 Mersilene suture (Ethicon, Sommerville, NJ).

The gastric remnant is anchored to the hiatus using interrupted 3-0 Mersilene sutures. Omentum from the greater curvature of the stomach is wrapped around the esophageal anastomosis and gastrotomy suture lines and anchored into position using interrupted Mersilene sutures. The diaphragm is repaired and the incision is closed in layers leaving one intercostal drain.

Postoperative care ensured optimal pulmonary function with chest physiotherapy, bronchodilators, and antibiotics when indicated. Subcutaneous heparin prophylaxis was begun preoperatively and continued until the patient was ambulatory. Parenteral nutrition was not used routinely before or after operation. Chest tubes were removed on the first or second postoperative day. Nasogastric tubes were left in place until aspirates were minimal, usually the second postoperative day. Water by mouth was begun on day 4, and diet advanced as tolerated.

Initially, the site of the lesion after diagnosis dictated the surgical approach; however, since 1983 we have attempted to resect all middle-third and lower-third tumors through a left thoracotomy. In total, 103 patients have been resected through a left thoracotomy: 76 by a left thoracoabdominal approach, and 16 using a Ivor Lewis technique. In 12 patients a left thoracotomy incision used for initial exploration required extension to a thoracoabdominal incision when exposure proved to be limiting.

Gastrografin swallows were not routinely performed unless a leak was suspected or difficulty had been encountered in performing the anastomosis. After discharge from the hospital, patients were seen at 3-month intervals for the first year, then every 6 months. They were evaluated for evidence of tumor recurrence, anastomotic stricture, and metastatic spread. Only patients complaining of dysphagia underwent esophagoscopy.

Statistical significance was determined using the χ^2 test. After exploratory data analysis [8], we felt that a multivariate analysis of our data would be misleading because the few stapler-related complications could be traced directly to identifiable technical problems.

Results

Since January 1980, 283 patients have been referred to us for treatment of esophageal cancer. Of these, 178 (62.8%) met our criteria for operation and underwent resection. In addition, 17 patients underwent resection for benign, nondilatable reflux-induced strictures causing unacceptable dysphagia. A total of 195 resections were performed using the EEA stapler. Of patients undergoing resection, 121 were men and 74 were women; the mean age of the entire group was 64.3 years (range, 33 to 84 years). Of 283 patients with carcinoma, 75 were older than 70 years and 208 were younger; 42 (56%) of the patients older than 70 years underwent resection versus 136 (65.4%) of those younger than 70 years (no statistical difference).

Operative mortality, defined as death within 30 days of operation, within the initial hospitalization, or as a result of operation, was 9.7% (19/195) for the entire group undergoing resection. Among patients older than 70 years, operative mortality was 13% (6/46); among those younger than 70 years, the mortality rate was 8.7% (13/149) (no statistical difference). Comparing the different incisions used, the operative mortality rate was 7.8% (8/103) in the left thoracotomy group, 11.8% (9/76) in the thoracoabdominal group, and 12.5% (2/16) in the Ivor Lewis group (no statistical difference).

Table 1. Pathological Diagnosis of 178 Patients Resected for Malignant Disease[a]

Tumor Type	No. of Patients	Full Thickness Penetration (%)	Lymph Node Involvement (%)	Positive Resection Margin (%)
Squamous cell	74	86	51	10.9
Adenocarcinoma	95	85	64	11.6
Undifferentiated cell carcinoma	5	80	40	0
Lymphoma	3	0	0	0
Oat cell	1	0	100	0
Total	178	81.4	64.9	10.7

[a] There were also 17 patients with benign peptic stricture.

Twenty-nine complications occurred in 25 patients, an incidence of 14.9% (29/195). Bronchopneumonia developed in 6 patients, and gastrotomy leaks, anastomotic leaks, and wound infections each developed in 4 patients. Three patients each experienced congestive heart failure (2 after myocardial infarction), atrial fibrillation, and postoperative chylothoraces. There was one episode of instrument failure and one deep venous thrombosis. Among patients older than 70 years, complications developed in 13% (6/46), whereas 15.4% (23/149) of patients younger than 70 years suffered hospital morbidity (not statistically significant).

In the left thoracotomy group, 16.5% (17/103) suffered complications, whereas 13.2% (10/76) of the thoracoabdominal group and 12.5% (2/16) of the Ivor Lewis group suffered complications (no statistical difference).

The majority of resections (n = 95) were performed for adenocarcinoma. Tumors extended through the entire esophageal muscle in 81.4% of patients, with 64.9% having positive lymph nodes and 10.7% having microscopic residual tumors at the resection margin (Table 1).

Patients were discharged home, on average, 13.6 days postoperatively (median, 11 days).

Postoperative dysphagia developed in 34 patients (19.3%). Dysphagia was caused by benign anastomotic narrowing of the stapled anastomosis in 24 patients (14.4%) and by recurrent tumor at the anastomosis in 10 patients (5.6%). By excluding from analysis those patients who died in the acute postoperative period (19) and those who developed recurrent tumor at the anastomosis (10), the true risk group for benign anastomotic narrowing was determined. Benign anastomotic narrowing developed in 8 of 46 patients (17.4%) at risk who were resected using the 25-mm stapling cartridge, in 14 of 83 (16.9%) resected

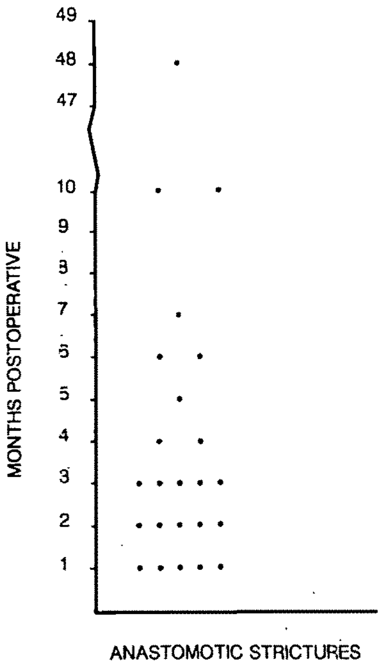


Fig 1. Time to occurrence of 24 strictures developing after the use of the end-to-end anastomotic stapler.

using the 28-mm stapling head, and in 2 of 31 (6.5%) patients resected using the 31-mm head; these differences were not statistically significant. The incidence of benign anastomotic stricture formation was much higher in patients initially resected for reflux-induced strictures (6/17 or 35.3%) than in those patients resected for malignant disease (18/149 or 12.0%) ($p < 0.05$). These results are similar to, but not exactly the same as, those reported previously in our first 176 patients [9].

The majority of strictures developed soon after operation: 83.3% (20/24) occurred within 6 months (Fig 1). The latest stricture developed 48 months postoperatively in a patient originally undergoing resection for benign peptic stricture. Overall, benign anastomotic strictures responded well to dilation; 75% (18/24) required two or fewer dilations to achieve normal swallowing (Fig 2). Three of 4 patients requiring more than three dilations were resected for benign disease. The 6 patients who developed dysphagia after resection for benign disease required 20 dilations, or 3.33 per patient, whereas the 18 patients originally resected for malignant disease averaged only 1.66 dilations per patient.

Follow-up was complete in 95% of patients to May 1988 (range, 2 to 96 months; average, 26.4 months); this was performed during May and June 1988. For malignant disease the 50% actuarial survival, including operative deaths, was 11 months, and at 2 years survival was 20%. Ten patients are still alive 5 years after operation for cancer (Fig 3).

Nine postoperative complications (4.6%) were related to the use of stapling instruments, including two operative deaths (1.0%). There were four anastomotic leaks (2.1%), four gastrotomy leaks, and one episode of instrument failure (0.5%). All four anastomotic leaks in our series occurred during a 13-month period beginning in February 1986, after 140 (72%) successful esophageal anastomoses had been performed.

We experienced three gastrotomy line leaks (including one death) before January 1984. Since then we have oversewn all straight gastric staple lines with a continuous, noninverting layer of 3-0 Mersilene. We have had only one further gastrotomy line leak, which occurred when an anterior gastrotomy was made within 1 cm of the stomach resection margin. At reoperation the tissue between the two staple lines had necrosed; despite an attempt to refashion the gastrotomy closure, this patient died.

In 7 patients (3.6%), the circular stapler cartridge tore the esophagus when too large a stapling head was inserted into a noncompliant esophagus. This occurred once with the 31-mm stapling head, five times with the 28-mm head, and once with the 25-mm head (no statistical difference). Three (43.0%) of these patients went on to develop an anastomotic leak, and 1 died. In the patient who developed a tear from the 25-mm head, an anastomosis was fashioned by hand; this was the only patient in whom we were unable to use the stapling instrument (0.5%).

The EEA stapler failed to work satisfactorily in 1 patient (0.5%). In this instance, although staples fired from the stapler, the knife failed to cut the center core of tissue. This was noted at the time of operation, and an attempt was made to trim the excess tissue through the gastrotomy. This patient was swallowing normally when she left the hospital. However, later recurrent dysphagia proved refractory to dilation and re-resection was eventually required. No patient required reoperation for bleeding, even though the left gastric artery was only tied and clipped with the LDS stapler.

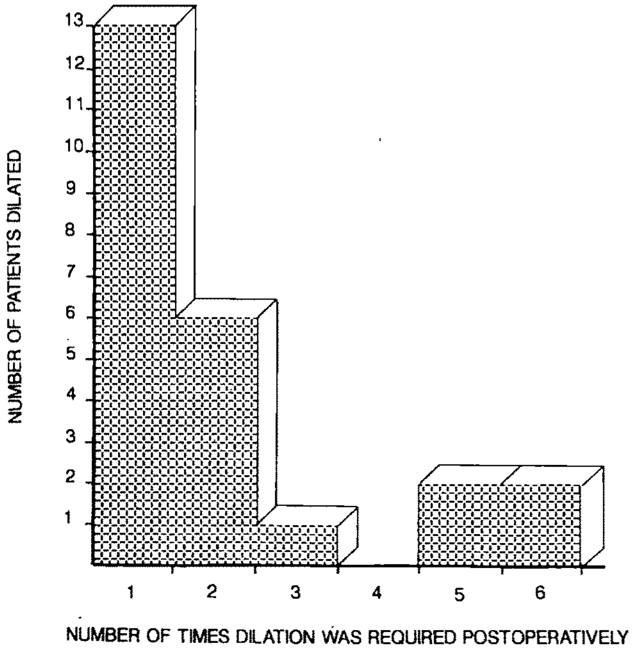
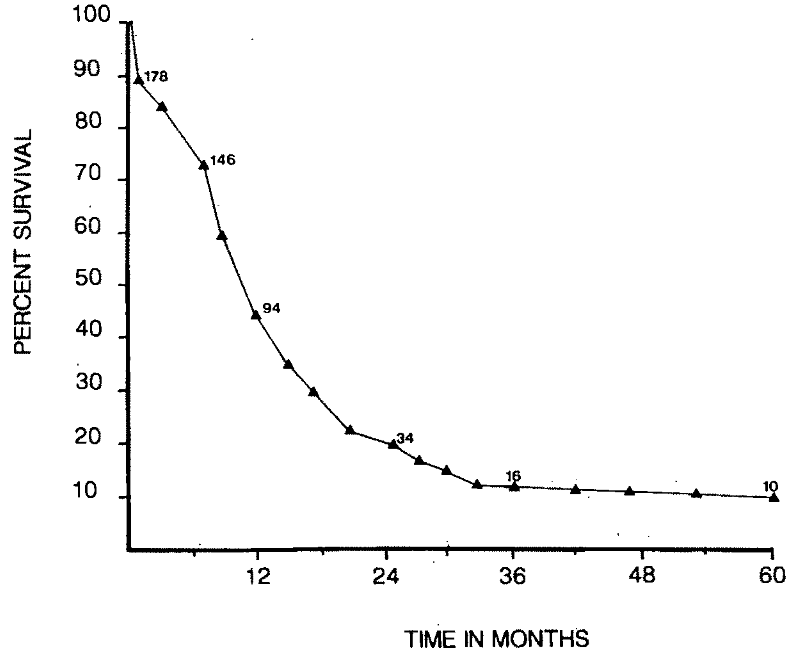


Fig 2. Number of times dilation was required per patient to relieve dysphagia.

Fig 3. Actuarial survival including operative death after esophagogastrectomy for cancer.



Comment

Our series confirms earlier reports that stapling instruments can be used safely to perform esophageal operations. Our data also clearly show that a learning curve and variability among surgeons are associated with the use of staplers for esophageal resection. Through experience, these technical and judgment errors can be identified and avoided. Based on our experience, we have modified our surgical technique in several ways.

Morbidity and mortality directly attributed to the use of stapling devices is low. The most serious stapler-related complication—anastomotic and gastrotomy leakage—resulted in two patient deaths (1.0%). In 7 patients, the proximal esophagus was torn after an attempt to insert too large a stapler head into a noncompliant esophagus. Even though an esophageal tear was noted in each case, and a further cuff of esophagus was excised to apparently normal tissue, 43% of these patients went on to develop an anastomotic leak. A more conservative approach in the selection of the EEA stapling head would have prevented the tearing in each case. Four anastomotic leaks occurred after considerable experience had been obtained using staplers and during a short period of time. This suggests that surgeon variability is an important determinate in the successful use of stapling instruments.

Because of the problems we have had with esophageal tears, we do not attempt to size the proximal anastomosis to determine which stapling cartridge to use. In 2 patients the esophagus was torn by the sizer; both of these patients developed postoperative leaks. We feel that this additional source of trauma is unnecessary; rather we advocate visually estimating the correct size of stapling head. With very little experience, one can accurately estimate the appropriate cartridge head to be used. If a tear does occur using the circular stapling device, a larger cuff of proximal esophagus than expected must be excised. Presumably, the mucosal tear runs farther than that in the outer muscle layer, and additional esophagus should be excised to compensate for this. We have not attempted to repair these tears with sutures for fear of incompletely approximating the mucosal component of the tear. Rather, we prefer to resect an additional length of esophagus and use the next smaller stapler head to reconstruct the anastomosis. Because of our confidence in the stapling devices we do not routinely hand sew anastomoses after an esophageal tear. Intraoperative methylene blue is often helpful in detecting tears of the esophagus in doubtful cases. We advocate performing a Gastrografin swallow on these patients and delaying oral feeding until a secure anastomosis has been demonstrated.

Overall, we found the circular stapler to be versatile and reliable. Only 1 patient could not undergo resection because the esophagus was too small to allow the safe insertion of the EEA stapler; this patient required a hand-sewn anastomosis. Similarly, in 1 patient the stapler failed to function correctly. This occurred in 1980, early in our experience, with an older, reusable model stapling gun. We have not seen this complication with the newer, disposable EEA stapler. Neither the TA nor the LDS staplers failed to perform correctly.

Our operative mortality rate (9.7%) compares favorably with those of previously published reports. In the review by Earlam and Cunha-Melo [10] of 122 papers published throughout the world between 1953 and 1978, the combined operative mortality was 29% (range, 1% to 83%) for patients undergoing esophageal resections. The circular stapling device has contributed to a lower mortality primarily by reducing the number of anastomotic leaks [5]. In a recent review of the surgical literature, Chaussin [1] reported a leak rate from sutured gastroesophageal anastomoses of 10% (range, 0% to 40%). Anastomotic leak rates using the EEA stapler are reported to be 1.4% (range, 0% to 5%) [5].

Since 1984 we have oversewn all gastrotomy suture lines with Mersilene after 1 patient died from a leak. We have seen this complication once since 1984, when it was caused by a technical error in placing the gastrotomy suture line too close to the gastric resection line; necrosis of the intervening stomach subsequently occurred. West and associates [4] reported gastrotomy line leaks developing in 2 of 31 patients after the use of stapling instruments and likewise advocated oversewing all gastric suture lines. As an added safety precaution, we strongly suggest wrapping all anastomotic staple lines and gastric staple lines with omentum. Moreover, care should be taken to place the gastrotomy far enough away from the gastric resection margin to ensure a viable segment of intervening stomach.

The primary goal of operation for benign and malignant esophageal obstruction is often the relief of dysphagia so that the patient can swallow once again. Of our patients undergoing resection using the EEA stapler, 19.3% experienced postoperative dysphagia. In the majority of these patients, benign anastomotic strictures caused the dysphagia. Although we were unable to demonstrate a statistically significant relationship between the size of the stapler head used and the incidence of benign stricture formation using the EEA stapler, our figures do suggest that a smaller anastomosis is more likely to become narrowed. Although we advocate using the largest possible stapler head, it is dangerous to be too ambitious.

By far the highest rate of stricture formation occurred in patients who underwent esophageal resection for reflux-induced strictures (35.3%). Orringer and Stirling [11] recently reported a similar incidence of dysphagia (50%) after cervical hand-sewn esophagogastric anastomoses in 91 patients for benign disease. We have previously reported the stricture rate in our first 176 patients [9]. As in our present series, the majority of these strictures developed soon after operation and responded well to one or two dilations. We concur with Orringer and Stirling that the stomach is the preferred organ for esophageal replacement.

We now attempt to perform all esophageal resections via a left thoracotomy. Our operative mortality improved from 11.8% in patients resected via thoracoabdominal incisions to 7.8% in patients explored exclusively via a left thoracotomy. Dark and co-workers [12] advocate a similar approach, although through the bed of the eighth rib, and have reported a similar operative mortality (7.6%). The left thoracotomy incision provided inadequate exposure in only 10% of our patients; furthermore, should the left thoracotomy provide inadequate exposure, the incision can be extended to a full thoracoabdominal incision. We agree with Dark and co-workers that the smaller incision reduces operative time and, as it does not cross the costal margin, allows for less painful coughing and breathing and better cooperation with physical therapy. We do not consider the thoracoabdominal incision a competitive, but rather a complimentary, incision.

Because of the relatively high operative mortality of esophageal resection, there has been a reluctance to operate on patients over 70 years of age [7, 13, 14]. These patients are thought to tolerate thoracotomy more poorly [15], to develop pulmonary emboli and myocardial infarction more frequently [16], and to have a higher operative mortality than younger patients undergoing esophageal resection [17, 18]. Our data refute this notion. Our hospital mortality in patients over 70 years of age was 13.0%, with 56% of patients with malignant disease undergoing resection. Among patients older than 75 years, the operative mortality was 6.3%. During the same period, our hospital mortality in patients younger than 70 years was not statistically different. Therefore, esophagectomy using stapling instruments can be performed successfully even in the elderly with an acceptable mortality.

In all groups, however, long-term survival remains elusive due to the advanced stage of presentation that characterizes esophageal cancer. We were unable to demonstrate improved survival using stapling instruments compared with historical controls [19]. Mediastinal invasion was seen in the majority of our patients, and this is reflected in our 5-year survival rates.

In conclusion, stapling instruments can be used safely and reliably to perform esophageal resections. Gastrotomy staple line leaks and anastomotic leaks are the major stapler-related complications. Oversewing all straight staple lines can reduce the incidence of gastrotomy line leaks, and the careful selection of circular stapling heads may avoid traumatizing the proximal esophagus. We feel it is better to err on the side of choosing too small a stapling head when performing the esophageal anastomosis because this may reduce the incidence of leaks, and future strictures are easily dealt with. Long-term survival does not appear to be improved by the use of stapling instruments.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1992 may begin the recertification process in 1990. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1990. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Right Ventricular Function and High-Frequency Positive-Pressure Ventilation During Coronary Artery Bypass Grafting

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The hemodynamic and respiratory consequences of two modes of ventilation, conventional intermittent positive-pressure ventilation with a frequency of 10 cycles/min and high-frequency positive-pressure ventilation at 70 cycles/min were investigated before and after cardiopulmonary bypass in 6 patients having coronary artery bypass grafting. All patients were adequately ventilated with each mode. During prebypass and postbypass periods, the group with high-frequency ventilation had significantly lower peak airway pressures ($p = 0.0001$) and mean airway pressure ($p < 0.05$). There were, however, no significant differences in right ventricular performance or pulmonary vascular resistance between the two modes of ventilation. No significant differences in other cardiovascular and respiratory variables were noted. High-frequency positive-pressure ventilation, with the advantage of quieter operating conditions and improved surgical access, can be safely applied when meticulous operation or hemostasis is required or during dissection of the internal mammary artery.

(Ann Thorac Surg 1989;48:263–6)

High-frequency positive-pressure ventilation (HFPPV) has been successfully used during anesthesia for bronchoscopy and laryngeal and thoracic operations [1]. High-frequency positive-pressure ventilation offers particular advantages because it improves effective gas exchange and cardiovascular stability with a markedly lower airway pressure than intermittent positive-pressure ventilation (IPPV) [1, 2]. This lower airway pressure with HFPPV may benefit right ventricular filling and decrease pulmonary vascular resistance, thereby improving right ventricular performance [3]. The application of HFPPV with a small tidal volume and a low airway pressure may also be useful during dissection of the internal mammary artery for patients undergoing coronary artery bypass grafting by providing a quieter operating field with minimal surgical interference. This study was designed to assess right ventricular performance and other hemodynamic and respiratory effects of HFPPV and IPPV in patients undergoing coronary artery bypass grafting.

Material and Methods

Six adult patients, aged 41 to 64 years (mean age, 56 years), undergoing coronary artery bypass grafting participated in this study, which was approved by the institutional review board. Five patients had experienced a myocardial infarction, and left ventricular ejection fractions were in the range of 39% to 65% (mean ejection fraction, 55.7%). All patients were premedicated with morphine sulfate (0.1 mg/kg) and scopolamine (0.04 mg/kg) intramuscularly. Before induction of anesthesia, a right internal jugular venous catheter and a right radial arterial catheter were inserted in each patient. A right ventricular ejection fraction/volumetric thermodilution pulmonary artery catheter (RVEF/PA catheter) was advanced to the pulmonary artery through the previously inserted right internal jugular catheter. Anesthesia was induced with a high dose of sufentanil (3 to 7 μg/kg) and vecuronium (0.3 mg/kg) and maintained with additional sufentanil, supplemental isoflurane (0.3% to 0.5%), and 100% oxygen.

Patients were first ventilated for a 15-minute interval with IPPV and then switched to HFPPV for the next 15-minute interval before the chest was opened in the prebypass period (IPPV-1, HFPPV-1). The same sequence of ventilatory modes (IPPV-2 and HFPPV-2) was repeated after closing the chest in the postbypass period. All patients were ventilated with the North American Dräger anesthesia ventilator (Narkomed-3). This ventilator was used to provide an IPPV mode with a tidal volume of 10 mL/kg, frequency rate of 10 cycles/min, inspiratory/expiratory ratio of 1:2, and fraction of inspired oxygen of 1. The Dräger machine also provided the HFPPV mode with expiratory tidal volume less than 200 mL, frequency rate of 70 cycles/min, inspiratory/expiratory ratio of 1:3.5, and fraction of inspired oxygen of 1. Actual delivered tidal volume with HFPPV, however, was less than 200 mL due to compliance of the anesthesia circuit.

Right ventricular performance was assessed with an American Edwards REF-1 cardiac output computer and a RVEF/PA catheter [4]. Using this REF-1 computer with a modified algorithm, Dhainaut and associates [5] reported a close correlation between right ventricular ejection fraction (RVEF) by thermodilution and RVEF by radionuclide angiocardiography. The method for calculating RVEF is as follows: a bolus of cool saline is injected into the right

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Table 1. Blood Gases and Peak Inspiratory Airway Pressure[a]

	Prebypass		Postbypass	
Variable	IPPV-1	HFPPV-1	IPPV-2	HFPPV-2
pH	7.46 ± 0.04	7.43 ± 0.04	7.46 ± 0.02	7.42 ± 0.04
$PaCO_2$ (mm Hg)	33.6 ± 4.7	37.4 ± 5.5	30.3 ± 2.2	35.0 ± 4.9
PaO_2 (mm Hg)	415 ± 50	443 ± 58	397 ± 183	385 ± 165
A-aDO_2 (mm Hg)	265 ± 48	234 ± 60	283 ± 183	293 ± 165
P_{PAW} (mm Hg)	20.3 ± 2.3	11.3 ± 1.5[b]	23.3 ± 2.9	12.8 ± 1.2[b]
PAW (mm Hg)	11.7 ± 1.8	7.5 ± 1.2[b]	14.5 ± 2.3	8.2 ± 1.3[b]

[a] Values are given as mean ± standard deviation. [b] Significance: $p < 0.05$ (IPPV vs HFPPV).

A-aDO_2 = alveolar-arterial oxygen tension difference; HFPPV = high-frequency positive-pressure ventilation; IPPV = intermittent positive-pressure ventilation; $PaCO_2$ = arterial carbon dioxide tension; PaO_2 = arterial oxygen tension; PAW = mean airway pressure; P_{PAW} = peak airway pressure.

atrium through the RVEF/PA catheter and mixed within the right ventricle with blood. The downslope of the thermal washout curve detected by the pulmonary artery thermister follows an exponential decay, which is interrupted by a series of diastolic plateaus. Calculation of the ratio between the temperature decreases of two successive diastolic plateaus yields an estimate of the residual fraction (the fraction of blood remaining in the ventricle). The ejection fraction is calculated as 1 − the residual fraction. The American Edwards REF-1 computer with modified algorithm determines the best fit for the exponential washout curve using least squares regression, and calculates the residual fraction by combining the measured interval between successive R waves from the electrocardiographic complex and the best-fit thermodilution curve. Cardiac output can also be calculated from the thermodilution curve. Right ventricular end-diastolic volume can be calculated as stroke volume divided by RVEF. Right ventricular end-systolic volume can also be calculated as right ventricular end-diastolic volume − stroke volume.

At the end of 15-minute intervals with IPPV and HFPPV in the prebypass and postbypass periods, the following variables were measured: cardiac index, stroke volume index, right ventricular end-diastolic volume index, right ventricular end-systolic volume index, RVEF, systemic and pulmonary vascular resistance indexes, central venous pressure, alveolar-arterial oxygen tension difference, pH, arterial carbon dioxide and oxygen tensions, peak airway pressure, and mean airway pressure. Values were expressed as the mean ± the standard deviation and statistical analysis was accomplished with analysis of variance and covariance, $p < 0.05$ being considered significant.

Results

Arterial blood gas values, peak airway pressures, and mean airway pressures are illustrated in Table 1, hemodynamic data in Table 2, and right ventricular performance in Table 3. All patients were adequately ventilated with conventional IPPV and Narkomed-3 HFPPV during the prebypass and postbypass periods of study. There were no significant differences in right ventricular performance, hemodynamic parameters, oxygenation, and CO_2 elimination between IPPV and HFPPV in the prebypass and postbypass periods. Peak airway pressures, however, were significantly lower with HFPPV than IPPV: 11.3 ± 1.5 mm Hg (HFPPV-1) versus 20.3 ± 2.3 mm Hg (IPPV-1) ($p = 0.0001$); 12.8 ± 1.2 mm Hg (HFPPV-2) versus 23.3 ±

Table 2. Hemodynamic Data[a]

	Prebypass		Postbypass	
Variable	IPPV-1	HFPPV-1	IPPV-2	HFPPV-2
MBP (mm Hg)	79.5 ± 9.5	83.5 ± 13.9	81.2 ± 11.1	82.5 ± 7.4
MPA (mm Hg)	14.2 ± 4.8	14.8 ± 5.8	14.0 ± 5.0	11.3 ± 4.8
CVP (mm Hg)	4.8 ± 2.6	5.7 ± 5.4	9.6 ± 4.5	7.7 ± 4.8
PCWP (mm Hg)	10.0 ± 4.4	10.1 ± 5.6	14.0 ± 5.0	11.3 ± 4.8
CI (L/min/m^2)	2.6 ± 0.52	2.68 ± 0.36	2.90 ± 0.60	2.67 ± 0.24
SVRI (dyne)	2336 ± 515	2308 ± 341	2020 ± 449	2385 ± 558
PVRI (dyne)	133 ± 84	118 ± 50	175 ± 67	197 ± 178

[a] Values are given as mean ± standard deviation.

CI = cardiac index; CVP = central venous pressure; HFPPV = high-frequency positive-pressure ventilation; IPPV = intermittent positive-pressure ventilation; MBP = mean blood pressure; MPA = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index.

Table 3. Right Ventricular Performance[a]

	Prebypass		Postbypass	
Variable	IPPV-1	HFPPV-1	IPPV-2	HFPPV-2
RVEF	0.54 ± 0.09	0.54 ± 0.08	0.48 ± 0.12	0.47 ± 0.07
SVI (mL/m^2)	46.2 ± 5.5	50.0 ± 9.0	28.8 ± 9.6[b]	30.5 ± 8.4[b]
RVEDVI (mL/m^2)	87.2 ± 14.6	86.5 ± 28.4	64.0 ± 18.1[b]	60.2 ± 16.2[b]

[a] Values are given as mean ± standard deviation. [b] Significance: $p < 0.05$ (prebypass vs postbypass).

HFPPV = high-frequency positive-pressure ventilation; IPPV = intermittent positive-pressure ventilation; RVEDVI = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; SVI = stroke volume index.

2.9 mm Hg (IPPV-2) ($p = 0.0001$). Mean airway pressure was also significantly lower with HFPPV ($p < 0.05$). In the postbypass periods stroke volume index and right ventricular end-diastolic volume index differed significantly ($p < 0.05$) from the values in the prebypass periods with both ventilatory modes.

Comment

A number of methods of high-frequency ventilation (HFV) have been evaluated during general anesthesia and in intensive care units since the introduction of HFPPV into clinical practice in 1971 [1]. Recently, HFPPV and high-frequency jet ventilation (HFJV) have been successfully used during anesthesia for bronchoscopy and laryngeal and thoracic operations [6]. High-frequency ventilation has the main advantages of providing effective gas exchange, cardiovascular stability, and preservation of renal function with a significantly lower airway pressure [7]. Usually, HFPPV is applied at ventilatory rates of 60 to 120 cycles/min with a small tidal volume of 2 to 4 mL/kg and a circuit system of low compliance. High-frequency jet ventilation is used at ventilatory rates of 100 to 300 cycles/min, and delivers jets of gas through the ventilating catheter with resulting air entrainment.

Recently, Normandale and colleagues [8] compared HFJV with conventional IPPV in 20 patients after aortocoronary bypass grafting and reported that hemodynamic effects of HFJV without added positive end-expiratory pressure were comparable with those of IPPV even though mean airway pressure was significantly lower with HFJV than with IPPV. Furthermore, HFJV was reported to be more beneficial in dogs with right ventricular dysfunction than conventional IPPV as increased cardiac output and decreased pulmonary vascular resistance were demonstrated with HFJV [9]. Cardiac output was also reported to be greater with synchronous HFJV than with IPPV or asynchronous HFJV in patients with congestive cardiomyopathy [10]. On the other hand, HFPPV was recommended for patients with respiratory failure in whom hemodynamic depression developed after they were treated with IPPV [11].

Pulmonary vascular resistance is lung volume dependent, and increasing airway pressure may increase pulmonary vascular resistance. During HFPPV, both lung volume and airway pressure are lower than in conventional IPPV. In most cases, increased pulmonary vascular resistance is a major factor in causing right ventricular failure. When pulmonary vascular resistance is elevated, the right ventricle must be capable of responding to increased load. Sibbald and co-workers [12] reported that right ventricular ejection fraction was inversely related to mean pulmonary artery pressure and that right ventricular end-diastolic volume increased with increasing pulmonary artery pressure but did not correlate with central venous pressure.

Right ventricular end-diastolic volume, when determined by the thermodilution method, is claimed to assess right ventricular preload more accurately than central venous pressure [13]. Recent studies have demonstrated that right ventricular function becomes increasingly important in patients undergoing coronary artery bypass grafting. Isolated right ventricular failure can cause hypotension, oliguria, and death [14]. Right ventricular systolic performance may influence overall systemic hemodynamics in patients with congestive heart failure and modulate left ventricular performance in acute illness [15, 16]. Overdistention of the right ventricle can shift the interventricular septum into the left ventricle and impair left ventricular filling [17]. During coronary artery bypass grafting, right ventricular function may be impaired by right ventricular ischemia due to coronary artery disease, by inadequate myocardial preservation due to inadequate cooling [18], by air emboli through the right coronary artery or vein grafts, or by acutely increased pulmonary vascular resistance due in part to a cardiopulmonary bypass effect [19].

Recently, conventional ventilators have been successfully used for HFPPV clinically and experimentally [20]. In this study, we demonstrated that HFPPV provided effective gas exchange and hemodynamic stability in patients having elective coronary artery bypass grafting, before and after cardiopulmonary bypass, when the chest was closed. We could not, however, demonstrate any significant improvement in right ventricular performance or decrease in pulmonary vascular resistance with HFPPV compared with conventional IPPV. Nor were there significant differences in other cardiovascular variables, oxygenation, or CO_2 elimination despite the significantly lower peak inspiratory airway pressure with HFPPV. Surgical access may be improved during HFPPV as smaller tidal volumes and airway pressures reduce surgical interference. This could be beneficial if intricate dissection of the internal mammary artery or meticulous hemostasis is required.

In conclusion, the ventilator of the standard Narkomed-3 anesthesia machine can safely provide HFPPV in addition to conventional IPPV. Although the surgical field may be improved, the lower peak airway pressures with HFPPV did not allow an improvement in right ventricular performance or pulmonary vascular resistance.

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Surgical and Endoscopic Palliation of Esophageal Carcinoma

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We reviewed the records of 732 patients with advanced esophageal carcinoma to determine the efficacy of palliative therapy. Palliative resection was performed in 156 patients. Hospital mortality was 9.6%, 1-year survival was 29.1%, and median survival was 7.8 months. Excellent or good palliative results were obtained in 78% of operative survivors. Bypass procedures were performed in 49 patients: hospital mortality was 20.4%, with a median survival of 6.2 months. Excellent or good palliative results were obtained in 71% of operative survivors. Intubation of the tumor was performed in 254 patients. Thirty-day mortality was 10.2%, and median survival was 4.0 months. No patient received excellent palliation. Neodymium:yttrium-aluminum-garnet laser therapy or photodynamic therapy was performed in 50 patients. No procedure-related deaths were recorded, and median survival was 4.1 months. Excellent or good results were obtained in 83% of patients. Lesser procedures were performed in 106 patients, and 117 had only staging examinations. Although surgical palliation of esophageal cancer with resection or bypass provides good results, the cost is high. Improvements in palliative results require reduction in operative mortality, increased accuracy of preoperative staging, continuing use of laser therapy, and increased use of chemotherapy alone or in combination with radiotherapy and operation.

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Some investigators consider operation as the treatment of choice for esophageal carcinoma [1–3]. When tumor spread is limited and a curative resection appears to be possible, this philosophy is defensible and treatment-related mortality rates less than 5% are common [1, 4, 5]. In contrast, there is no agreement on the optimal treatment of patients who have more advanced disease with less chance of cure. Many surgeons continue to recommend an aggressive surgical approach to both prolong survival and provide palliation, either by resection of the tumor [6] or, in patients in whom resection is technically impossible, through a bypass procedure [7]. Other options include endoscopic procedures such as intubation or laser therapy. To evaluate surgical and endoscopic palliation in patients with incurable esophageal carcinoma, we reviewed the combined experiences of the University of Padua and the University of Chicago.

Material and Methods

Patient Population

Between 1978 and 1986, 1,232 unselected patients with primary esophageal carcinoma were evaluated by the Department of Surgery of the University of Padua or the University of Chicago. Patients with adenocarcinoma of the gastric cardia were excluded. Nineteen patients had adenocarcinoma limited entirely to the tubular esophagus, although the cause, Barrett's epithelium or otherwise, was not defined. A retrospective review of hospital records was performed, and follow-up to December 1987 was obtained. Data on age, sex, race, concomitant diseases, histology, site and stage of tumor, type and intent of treatment, extent of lymph node dissection, postoperative complications and mortality, and evidence of recurrence or metastases were specifically sought in each instance. Clinical and pathological staging was performed according to the TNM classification system of the International Union Against Cancer 1987 [8].

Statistical Analysis

Survival statistics were calculated by the Kaplan-Meier actuarial method. Deaths due to all causes, including perioperative causes, were included in the survival analysis. The quality of palliation was evaluated according to the patient's ability to swallow and classified as follows: (1) excellent, able to eat a normal diet; (2) good, able to eat a normal diet but experiencing occasional dysphagia; (3) fair, able to swallow only liquids; (4) poor, severe or total dysphagia.

Resections were classified as either palliative, indicating that some tumor was not removed, or curative, indicating that all identifiable carcinoma was completely resected. In this sense, 505 patients (40.8%) underwent a complete resection with curative intent. Of the other 732 (59.2%) patients, 671 from Padua and 61 from Chicago, 509 were treated with major surgical or endoscopic procedures

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Table 1. Palliative Procedures

Procedure	No. of Patients[a]
Palliative resection	156 (21.3)
Bypass operation	49 (6.7)
Intubation	254 (34.7)
Laser therapy	50 (6.8)
Lesser procedures	106 (30.5)
Medical treatment	117
Total	732

[a] Numbers in parentheses are percentages.

(Tables 1, 2), and they are the subject of this paper. The remaining 223 received lesser surgical procedures (eg, feeding gastrostomy, dilations) or only nonsurgical treatments.

Results

Palliative Resections

In 156 patients, a palliative resection, as defined by the inability to remove all cancer, of primary tumor alone or of tumor and involved lymph nodes was performed. The mean age was 56.8 years (range, 34 to 78 years); 123 patients were men and 33 were women. The primary tumor was located in the cervical esophagus in 13 patients, in the upper thoracic esophagus in 34, in the middle thoracic esophagus in 75, and in the lower thoracic esophagus in 34. One hundred forty-seven patients had squamous cell carcinoma, 4 had adenocarcinoma, 2 had oat cell carcinoma, 2 had adenosquamous carcinoma, and 1 had anaplastic carcinoma. The pathological staging was stage II in 6 patients; stage III in 105, and stage IV in 45. The reasons why curative resection was not possible and the types of postresection reconstruction are summarized in Tables 3 and 4, respectively. The stomach was used for reconstruction in 139 patients (89.1%), and the colon and the jejunum were used in 11 and 4 patients, respectively. In 65 (76.4%) of 85 procedures with a cervical anastomosis, the esophagectomy was performed through a transthoracic approach; in the other 20 cases, a transhiatal esophagectomy was performed.

There were 20 anastomotic leaks (12.8%), 19 in a cervical anastomosis, which were associated with marginal necrosis of the interposed stomach in 4 patients. Ten patients required one or more reoperations; the other 10 were treated with drainage, antibiotics, and parenteral nutrition. Leak-related mortality was 20.0% (4/20). In all, 72 patients (46.1%) had postoperative complications, and 15 of them had one or more reoperations. The hospitalization time ranged from 10 to 133 days with an average of 22.6 and a median of 17 days. The overall hospital mortality was 9.6% (15/156) and was similiar for patients in Padua (8.9%) and Chicago (16.1%) (p = NS).

Table 2. Type of Treatment and Site of Esophageal Tumor

Treatment	Cervical	Thoracic Upper	Thoracic Middle	Thoracic Lower	Total
Resection	13	34	75	34	156
Bypass	3	10	24	12	49
Intubation	1	56	126	71	254
Laser	4	12	23	11	50
Total	21	112	248	128	509

Table 3. Reason for Noncurative Resection of Esophageal Cancer

Disease Status	No. of Patients[a]
Advanced local disease	112 (71.8)
Tracheobronchial invasion	30
Other	82
Nodal metastasis	18 (11.5)
Positive resection margin	16 (10.3)
Liver metastases	1 (0.6)
Other	9 (5.8)
Total	156

[a] Numbers in parentheses are percentages.

Seventy patients (44.8%) were treated with radiation therapy alone or with radiation therapy plus chemotherapy. These therapies were performed as part of different regimens, and evaluation is impossible.

The actuarial survival rate of all patients, not just operative survivors, was 29.1% at 1 year, 8.5% at 2 years, and 2.9% at 3 years; median survival was 7.8 months. In patients receiving adjuvant therapy, survival was 44% at 1 year, 13% at 2 years, and 5% at 3 years. In contrast, survival in patients receiving no adjuvant therapy was 17% at 1 year, 7% at 2 years, and 3% at 3 years. Despite the disparity at 1 year, these survival rates are not significantly different (p = NS).

Follow-up was available in 100 of 141 survivors between 1 and 3 months after operation. Of these, 41 (41%) were able to eat a completely unrestricted diet and were judged to have had excellent palliation. Good palliative results

Table 4. Reconstruction After Palliative Resection

Reconstruction	No. of Patients[a]
Cervical esophagogastrostomy	77 (49.4)
Thoracic esophagogastrostomy	57 (36.5)
Cervical esophagocolostomy	8 (5.2)
Pharyngogastrostomy	5 (3.2)
Thoracic esophagojejunostomy	3 (1.9)
No reconstruction	2 (1.3)
Thoracic esophagocolostomy	2 (1.3)
Free-loop jejunum transplantation	1 (0.6)
Pharyngocolostomy	1 (0.6)
Total	156

[a] Numbers in parentheses are percentages.

were obtained in 37 (37%) patients, and 14 and 8 patients were classified as having fair or poor results.

Bypass Operations

In 49 patients in whom complete resection was technically impossible, a bypass procedure was performed. The mean age was 54.1 years (range, 36 to 70 years); 42 patients were men and 7 were women. The primary tumor was located in the cervical esophagus in 3 patients, in the upper thoracic esophagus in 10, in the middle thoracic esophagus in 24, and in the lower thoracic esophagus in 12. Results of histological examination were available in 47 patients; there were 40 squamous cell carcinomas, six adenocarcinomas, and one anaplastic carcinoma. Clinical staging was available in 40 cases and was stage III in 23 and stage IV in 17. Distant metastases were detected in 8 patients. Twenty-five patients had tracheobronchial invasion, with or without an esophagorespiratory fistula.

Cervical esophagogastrostomy was performed in 37 patients, cervical esophagocolostomy was performed in 11 patients, and thoracic esophagogastrostomy was performed in 1 patient. The incidence of anastomotic leak or organ necrosis was 32.6% (16/49) and 2.1% (1/49) for cervical esophagogastrostomy and cervical esophagocolostomy, respectively. Major postoperative complications occurred in 28 patients, with an operative morbidity rate of 57.1%; in 15 patients, one or more reoperations were performed. The hospital mortality rate was 20.4% (10/49). Radiation therapy was used in 26 patients (53.0%), radiation therapy plus chemotherapy was used in 3 patients, and chemotherapy alone was used in 6 patients. As with the previous group, these treatments were performed with different regimens and evaluation is impossible. Of the 39 patients discharged from the hospital, 28 were evaluable for follow-up between 1 and 3 months after operation. The quality of palliation was estimated as excellent or good in 20 patients (71%), fair in 3 patients, and poor in 5 patients. Median survival was 6.2 months, and only 3 patients lived more than 1 year.

Intubation

Pulsion or traction intubation of the tumor was performed in 215 and 39 patients, respectively. Pulsion intubation was performed in sedated patients. The tumor was dilated over a guidewire with Savary or Celestin dilators. The tube, most frequently the Celestin variety, was then inserted with the Savary introducer. Traction intubation required a general anesthetic for a laparotomy. The tumor was dilated through a gastrotomy, and a tube was passed through the mouth and then pulled into place from below.

The site of the primary tumor was the upper thoracic esophagus in 56 patients, the middle thoracic esophagus in 126 patients, and the lower thoracic esophagus in 71 patients. In 1 patient, who previously underwent laryngectomy, the tumor was located in the cervical esophagus. Histology was available in 215 patients; there were 205 squamous cell carcinomas, eight adenocarcinomas, and two adenosquamous carcinomas. The clinical staging of these patients was stage II, 120 patients; stage III, 86 patients; and stage IV, 39 patients. The morbidity of these procedures is summarized in Table 5. Most of these patients were treated on an outpatient basis; the other patients were hospitalized for a mean of 10 days. Often they were treated in a terminal condition and died of neoplastic cachexia shortly after the procedure. The hospital mortality rate for endoluminal prosthesis placement was 3.1%, and the 30-day mortality rate was 10.2%.

Table 5. Hospital Morbidity After Intubation for Esophageal Tumor

	Type of Intubation[a]	
Morbidity	Pulsion (n = 215)	Traction (n = 39)
Displacement	20 (9.3)	3 (7.7)
Obstruction	3 (1.4)	0
Perforation	10 (4.6)	2 (5.1)
Bleeding	3 (1.4)	1 (2.5)
Total	36 (16.7)	6 (15.3)

[a] Numbers in parentheses are percentages.

It is difficult to assess the quality of palliation in this group of patients. In fact, because of their poor general condition, few patients returned for follow-up. Almost all patients were able to swallow a liquid or a soft diet, but to avoid the risk of obstruction, a solid diet was never attempted. The actuarial survival rate was 6.6% at 1 year and the median survival was 4.0 months.

Laser Therapy

Laser therapy was performed in 50 patients: 41 underwent neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy with a Cooper Lasersonic Model 8000, and 9 patients were treated with photodynamic therapy. For the Nd:YAG laser treatments, the patient was sedated and the stenosis was dilated. The endoscope was then passed, and a retrograde technique was used with the laser beam (power setting, 20 to 100 W) directed circumferentially. For photodynamic therapy, an argon-dye laser, Meditec MDS Model 90, was used. Hematoporphyrin was administered intravenously at 5 mg/kg; 48 hours later, a quartz waveguide fiber was passed through an endoscope and the tumor was irradiated.

The ages ranged from 46 to 79 years with an average of 65 years; 42 patients were men and 8 were women. In 23 patients, the contraindication to operation was tumor related: advanced local disease in 14 patients, lymph node involvement in 5 patients, liver metastases in 2 patients, and other causes in 2 patients. In the other 27 patients, operation was not performed due either to poor general condition alone or to poor general condition and concomitant diseases. The primary tumor was located in the cervical esophagus in 4 patients, in the upper thoracic esophagus in 12, in the middle thoracic esophagus in 23, and in the lower thoracic esophagus in 11 patients. In 49 patients the histology of the tumor was squamous cell carcinoma; in the remaining patient the histology was adenocarcinoma.

In the 41 patients treated with the Nd:YAG laser, the

Table 6. Therapy Complications of Neodymium: Yttrium-Aluminum-Garnet Laser in 41 Patients

Complication	Early	Late
Perforation	3	. . .
Bleeding	1	1
Tracheobronchial fistula	. . .	2
Mediastinal fistula	. . .	1
Total	4 (9.7%)	4 (9.7%)

mean length of the stenosis was 6.3 cm (range, 1 to 12 cm) and the mean diameter was 6.5 mm (range, 2 to 9 mm). The mean improvement in diameter after treatment was 8 mm. Tumor dilation with the retrograde laser technique was used in almost all patients. The average number of treatments for each patient was 3.1 (median, 3) and ranged from one to 17 with four early (9.7%) and four late complications (9.7%) (Table 6). In 30 patients available for follow-up, the quality of palliation was evaluated as excellent or good in 25 patients (83.3%) and fair in 5. There were no poor results, and median survival was 4.1 months. Of the 9 patients treated with photodynamic therapy, the mean tumor length was 5.2 cm (range, 2 to 9 cm), and 7 patients received only one laser treatment. Only 4 had a serious esophageal stenosis, and in 3 good palliation of dysphagia was observed. No complications were recorded in the patients treated with photodynamic therapy.

Comment

Because carcinoma of the esophagus is typically advanced at the time of diagnosis, treatment is usually palliative and is associated with one of the lowest survival rates of all solid tumors. In contrast to the Japanese experience [9], in the Western world early detection is unusual. Treatment is widely debated, and perhaps for no other malignancy is there so much disagreement. For many surgeons palliation of dysphagia is the only reasonable therapeutic goal [10], and even aggressive surgeons recognize that only patients with relatively limited disease, as determined by preoperative and intraoperative staging, are candidates for extensive, curative operations [11].

This report contains an amalgam of patients from two institutions. Our motive is to present a sufficiently broad experience so that some insight into all palliative options may be obtained. This is obviously not a prospective study and cannot be thought to prove the superiority of any single approach. Rather, it is a retrospective analysis that does provide results, of different therapeutic options, that can be used in formulating therapeutic strategies.

A variety of procedures are used to palliate the patient whose disease is too extensive for curative therapy or whose physiological condition is too poor to permit extensive operation. The intent of palliative treatment is to mitigate or improve the major symptoms and delay related complications due to disease progression. The treatment should be as simple as possible, with minimal morbidity and mortality, to allow patients to remain outside the hospital and enjoy their short life span. The selection of the method of palliation is difficult because no technique is suitable for all patients. The choices depend on the site and extent of the tumor, the experience and aggressiveness of the physician, and the quality of life desired by the patient.

Palliative resection, when technically possible, is believed by many surgeons not only to provide the best palliation but to be the treatment of choice for all patients with esophageal carcinoma [5, 6]. Palliation means relief not only of dysphagia but also of sepsis, hemorrhage, tendency to pulmonary aspiration, and risk of fistulization into the tracheobronchial tree, which can be achieved surgically only by esophagectomy [6]. Unfortunately, comparison of the reported results of palliative esophagectomy is very difficult. The intent, curative or palliative, of a procedure is inevitably subjective, and few surgeons separate their procedures according to complete versus incomplete cancer removal. In some series, there is no division [5, 6], whereas in others the resections are termed "real curative," "probably curative," "palliative," and "cleaning procedures" [12]. Because different results are obviously expected in patients with early versus advanced disease, higher operative mortality rates and worse results occur when esophagectomy is routinely performed than when only candidates for a curative procedure are treated. In our series, surgical resection was used as a palliative treatment in 23.6% (156/661) of resected patients. Most patients treated with palliative resection were in good general condition and were believed to be candidates for curative operation on the basis of preoperative staging. The decision to perform palliative esophagectomy was made intraoperatively, when a complete resection was impossible. This group has the most favorable prognosis in our series from the standpoint of surgical risk. It is therefore difficult to determine if their better survival as compared with that of patients receiving alternative palliative procedures is due to more effective surgical therapy or to a better general preoperative status. In this group with relatively favorable prognosis, morbidity and mortality rates were not inconsiderable, 46.1% and almost 10%, respectively. On the other hand, although the median survival was only 7.8 months, ability to swallow was excellent or good in nearly 75% of evaluable patients and poor in only 7%.

From these data, it is difficult to draw absolute conclusions. Palliative resection improves the quality of life but does not greatly prolong survival and carries relatively high morbidity and mortality rates. The improving results of alternative treatments such as laser therapy and the combination of chemotherapy and radiation therapy [13–15] may soon prove these modalities, alone or in combination with operation, to be preferable to palliative resection alone.

The rationale for esophageal bypass is to relieve dysphagia with a simple operation, avoiding the morbidity of a thoracotomy and an intrathoracic esophageal anastomosis. These procedures are performed when resection is technically impossible and the surgical risk for the patient is not unreasonable. Although some surgeons report good results [7], operative mortality rates are highest of all palliative procedures performed for esophageal carcinoma, ranging from 24.0% [16] to 41.5% [17]. On the other hand, the quality of palliation in survivors is good and similar to that achieved in the group of palliative resections.

In light of these high morbidity and mortality rates, we believe that a bypass can be considered only when a malignant respiratory fistula is present. Intubation provides only fair or poor palliation of this devastating complication, as the fistula is usually not totally occluded. Whenever the patient's general condition is still relatively good and there is no evidence of distant metastases, an esophageal bypass can provide good palliation [18]. Development of a malignant respiratory fistula has a major influence on survival in patients with esophageal carcinoma, and such patients have a median survival of 4 to 5 months if the fistula is controlled [18].

Endoscopic intubation of the tumor can be performed with a short hospitalization or on an outpatient basis [19]. Because general anesthesia is not necessary, intubation is particularly useful in high-risk patients. Our relatively high 30-day mortality rate of 10.2% is explained by the preterminal condition of most of these patients; death is rarely procedure related. On the other hand, implantation of a tube does not always satisfactorily improve the quality of the patient's life. It allows only a liquid or semiliquid diet and is technically impossible when the tumor extends within 4 cm of the cricopharyngeal sphincter or when deviation of the esophageal axis is present at the gastroesophageal junction. This procedure represents a simple method of restoring a partial ability to swallow in preterminal patients in poor general condition.

Our results with endoscopic laser treatment are encouraging and comparable with previous experiences [20, 21]. This procedure has a low mortality and morbidity rate and requires only brief hospitalization. The palliation of dysphagia is better than that achieved by intubation; however, restenosis occurs within 6 weeks, requiring repeated treatments. The procedure can be performed in combination with other therapies. In a series of 93 patients treated by a combination of Nd:YAG laser therapy and intracavitary radiation, there was a 12.2% incidence of complications, a 2.1% mortality rate, and a median survival of 7.4 months, with 71% of the patients free of dysphagia until their death [15]. Endoscopic Nd:YAG laser therapy is an effective palliative modality, and more innovative protocols involving chemotherapy and radiation therapy are needed.

In conclusion, all possibilities should be considered for patients with incurable esophageal carcinoma to provide the best quality of life with the minimum risk of complications. The morbidity and mortality rates of palliative resection do not support this procedure as a systematic palliative approach for all patients: it should be performed only when incurable disease is not identified until operation. When incurable or unresectable disease is found preoperatively, alternative treatments, such as intracavitary irradiation, radiotherapy, chemotherapy, and laser therapy can achieve comparable survival rates, as well as quality of palliation, with less morbidity and mortality. The risks of an esophageal bypass should be accepted only when an esophagorespiratory fistula exists and no other realistic alternatives are available.

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Value of Fiberoptic Bronchoscopy and Angiography for Diagnosis of the Bleeding Site in Hemoptysis

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We evaluated 36 patients during active hemoptysis and compared the diagnostic yield of different procedures. Twenty-seven patients (75%) had one or more previous episodes of hemoptysis, most of which were not massive. Fiberoptic bronchoscopy was performed in 25 patients, and the bleeding site was identified in 17 (68%). The likelihood of localizing the bleeding site was significantly higher with early versus delayed fiberoptic bronchoscopy (91% versus 50%). Bronchial arteriography was performed in all 36 patients; positive arteriographies were observed in 20 cases (55.5%). Arteriography was positive in only 2 of the 8 cases in which fiberoptic bronchoscopy did not localize the site of bleeding. Bronchial artery embolization was successfully performed in 10 patients. However, the bleeding recurred within the first week after embolization in 2 patients, and 1 of them died.

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One of the most demanding diagnostic problems is identification of the bleeding site for surgical control of massive hemoptysis. Occasionally, only the hemorrhaging lung can be localized, but this is of little value when one performs pulmonary resection. Early diagnostic procedures may increase the likelihood of identifying the bleeding site. We reviewed the management of 36 patients during active hemoptysis, with particular attention to evaluating the efficacy of various diagnostic modalities.

Material and Methods

Thirty-six hospitalized patients with hemoptysis of nonneoplastic origin were studied between January 1979 and December 1984. There were 29 men and 7 women with a mean age of 51 years.

Fourteen patients had bronchiectasis, 12 exhibited sequelae to tuberculosis, and 4 had active tuberculosis (positive sputum culture). Two other patients had arteriovenous fistula and silicosis, respectively. In the remaining 4 patients, the underlying disease was unknown.

Three patients bled more than 600 mL/24 h; 9 patients had losses between 300 and 600 mL/24 h, and 10 had losses between 100 and 300 mL/24 h. The daily quantity of hemoptysis could not be estimated in 14 patients. Distribution of patients according to cause of hemoptysis and quantity of bleeding is presented in Table 1.

Twenty-seven patients (75%) had one or more previous episodes of hemoptysis, most of which were not massive. In all cases, a selective bronchial arteriography was performed with 6F to 7F catheters and nonosmotic hydrosoluble iodine contrast agent. "Positive" arteriographies were those in which the pathological findings were limited to only one pulmonary lobe. In 10 patients with severe hemoptysis at the time of arteriography in whom the bleeding site was accurately identified because of extravasation of contrast medium and/or the presence of bronchopulmonary shunts (7 patients), and/or hypertrophy and hypervascularization of the bronchial artery (3 patients), embolization was performed using a fibrin sponge. Anterior spinal arteries were never visualized.

In 25 patients, fiberoptic bronchoscopy was performed under local anesthesia with the Olympus model BFB3. Bronchoscopic examination was considered positive only if it identified the lobe or segment from which the bleeding originated; it was considered negative when only the side of bleeding was localized or when bilateral or unilateral blood remnants without persistent hemorrhage in either lobe were observed. Early fiberoptic bronchoscopy, ie, within 24 hours after the onset of hemoptysis, was performed in 11 patients. In the remaining 11 patients, fiberoptic bronchoscopy was not performed because of technical difficulties, excessive delay after bleeding had subsided, or patient's refusal. A complete bronchographic examination was performed in 8 patients. In addition, chest roentgenograms were evaluated in all cases.

Results

Fiberoptic Bronchoscopy

In 17 patients (68%), the bleeding site was identified by fiberoptic bronchoscopy. In 13 of 17 patients with positive bronchoscopic examination, the bleeding site coincided with the suspicious image on the chest roentgenogram. The likelihood of localizing the bleeding site was significantly higher with early versus delayed fiberoptic bronchoscopy (91% versus 50%) (Table 2).

Bronchial Arteriography

Bronchial arteriography was considered abnormal when hypervascularization, vascular hypertrophy, aneurys-

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Table 1. Distribution of Patients According to Cause and Quantity of Hemoptysis

	Blood Loss (mL/h)				
Cause	>600	300–600	<300	Non-measurable	Total
Active tuberculosis	2	. . .	2	. . .	4
Sequelae to tuberculosis	. . .	5	2	5	12
Bronchiectasis	1	2	4	7	14
Arteriovenous fistula	. . .	1	. . .	. . .	1
Silicosis	. . .	. . .	1	. . .	1
Unknown	. . .	1	1	2	4
Total	3	9	10	14	36

matic and angiomatous formations, bronchopulmonary fistulas, and bronchial extravasation of the contrast agent were observed.

Abnormal arteriographies were observed in 31 of 36 patients (86%), but arteriography was considered "positive" in only 20 patients (64.5%). Seven of the nine early arteriographic examinations performed within 24 hours after the onset of hemoptysis were positive.

Correlation Between Bronchoscopy and Arteriography

When positive arteriographies were compared with chest roentgenograms, the affected area was strictly coincidental in 16 cases; thus, in these cases, the bronchial arteriography did not identify a bleeding site different from that suspected by chest roentgenogram.

Arteriographic and bronchoscopic findings coincided in 11 of the 17 patients in whom the bleeding site was identified by fiberoptic bronchoscopy. Of the 6 noncoincidental cases, a normal arteriography was demonstrated in 3, bilateral abnormal arteriographic findings were demonstrated in 2, and unilateral abnormal arteriographic findings affecting the whole lung were demonstrated in 1.

Arteriography was positive in only 2 of the 8 patients in whom fiberoptic bronchoscopy did not localize the site of bleeding. In the remaining 6 patients, arteriographic findings were pathological (bilateral in 5 and unilateral in 1).

Bronchial arteriography performed in the 25 patients who also underwent fiberoptic bronchoscopy proved to be a useful diagnostic tool before operation in only 2 patients (Table 3).

Bronchography

Bronchographic examination was also performed in 4 of the 17 patients in whom fiberoptic bronchoscopy identified the site of bleeding. In 2 of these 4 patients, bronchoscopic, bronchographic, and arteriographic findings coincided; in the other 2 patients with noncoincidental data, bronchial arteriography was negative.

Bronchography was useful in localizing the site of bleeding in 4 of the 8 patients with negative fiberoptic bronchoscopy. In these 4 patients, arteriographic findings were abnormal, although "negative."

Table 2. Results of Fiberoptic Bronchoscopy in 25 Patients With Hemoptysis

	Time of Bronchoscopy	
Result	Early (n = 11)	Delayed (n = 14)
Active bleeding observed	10 (91%)	7 (50%)
Side localized	1	7

Comment

Clinical signs useful for determination of the severity of hemoptysis are not easy to establish. Quantitative criteria for defining arbitrarily the timing of operation in patients with active hemoptysis vary between 240 and 600 mL/24 h to as much as 1,000 mL/8 days [1–8]. In most of the present patients it was difficult to assess bleeding rates before admission to the hospital. Only 3 patients in this series bled more than 600 mL in 24 hours [9]. The patients who underwent operation were those who bled uninterruptedly during the next 24 hours after admission, who had rapid flooding of the tracheobronchial tree after the initial bronchoscopy and washings, or those with both conditions.

Bronchial arteriography was particularly valuable in the 10 cases in which embolization procedure was feasible. In these the purposes of bronchial artery embolization were to achieve immediate control of bleeding and to improve clinical conditions for a prospective operation. According to other investigators [2, 3, 6], the safe period of time before revascularization after bronchial artery embolization is approximately 4 weeks, with a 22.2% to 71% rate of recurrent bleeding. In our series, however, the bleeding recurred within the first week after embolization in 2 patients, and 1 of them died.

Bronchial arteriography identified the bleeding site in 55.5% of patients, whereas fiberoptic bronchoscopy achieved the same result in 68% of patients. Arteriography was useful in only 2 of the 8 patients with negative bronchoscopic findings. In the remaining 23 patients, arteriography did not lead to a change in the prefiberoptic bronchoscopy diagnoses. Therefore, we consider the main advantage of angiography to be in the context of bronchial artery embolization. Patients should be referred for embolization after clinical and endoscopic evaluation.

Bronchographic examination cannot be performed during the acute bleeding episode. In the present study,

Table 3. Correlation between Fiberoptic Bronchoscopy and Bronchial Arteriography in 25 Patients

Results of Arteriography	Results of Bronchoscopy	
	Positive	Negative
Positive	11	2
Negative	6	6
Total	17	8

bronchography yielded more diagnostic information than a delayed bronchial arteriography. Therefore, the indication of arteriography in the remission period does not appear to add any additional information to that obtained by bronchographic examination.

Endoscopic and arteriographic findings frequently coincided with the "suspicious" areas already detected on chest roentgenograms. Our results are comparable with those reported by Fellows and associates [1] in 6 patients with cystic fibrosis and massive hemoptysis; in most cases, the combination of chest roentgenograms and fiberoptic bronchoscopy is considered potentially diagnostic for bleeding site and treatable surgical approach.

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Symptomatic Visual Deficits After Open Heart Operations

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Symptomatic visual deficits occurred in 4 patients in a series of 700 open heart operations performed by one of us (D.M.S.). The causes of these deficits were retinal emboli, occipital lobe infarction, and anterior ischemic optic neuropathy. The pathophysiology and clinical presentation of these complications are discussed, and previous reports of postoperative visual complications are reviewed.

(Ann Thorac Surg 1989;48:275–9)

Neurological deficits are serious and not infrequent complications of open heart operations. These include injuries of the brachial plexus and peripheral nerves, the cranial nerves, and the central nervous system [1–6]. Of the latter, visual deficits are uncommonly reported despite evidence that the eye and visual pathways may be sites within the central nervous system most frequently affected by open heart operations [1]. This discrepancy results from the effect of medications and the intensive care environment on the perception of visual loss, the lack of careful preoperative and postoperative ocular examinations, and the often silent nature of the injury.

In a retrospective survey of 700 adult patients who underwent open heart operations, including coronary artery bypass grafting and valve replacement procedures, and who were operated on by one of us (D.M.S.), 4 patients had symptomatic postoperative visual deficits. The cause of the visual loss in these patients is presented, together with a review of the literature describing these complications.

Case Reports

Patient 1

A 71-year-old woman had critical aortic stenosis and an 80% blockage of the left main coronary artery. Because of unstable angina, the patient underwent placement of an intraaortic balloon pump, followed by urgent aortic valve replacement and triple-vessel coronary artery bypass grafting. In the immediate postoperative period, profound low cardiac output syndrome developed that required support with multiple inotropic agents.

At the time of extubation on the fourth postoperative day, the patient reported a profound visual defect in the left eye and some loss of vision in the right eye. There were no other neurological deficits. A computed tomographic scan of the brain showed generalized cortical atrophy but no evidence of an infarct. Noninvasive studies of the carotid arteries revealed no stenotic lesions. Ophthalmologic evaluation revealed bilateral ischemic optic neuropathy and retinal emboli to the left eye. The patient recovered completely from the cardiac operation but had no improvement of the visual deficit. The patient has adapted well to the near-total visual loss in the left eye and leads a normal life 2 years after operation.

Patient 2

A 60-year-old man had a 2-month history of crescendo angina and a markedly positive exercise tolerance test. Cardiac catheterization revealed an 80% obstruction of the left main coronary artery and 100% obstruction of the right coronary artery. Triple-vessel coronary artery bypass grafting was performed.

On the second postoperative day, the patient noted an altitudinal defect, affecting the superior portion of the visual field, in the right eye. Noninvasive studies of the carotid arteries and a computed tomographic scan of the brain were performed, and findings were normal. The results of ophthalmologic evaluation were consistent with a diagnosis of nonarteritic ischemic optic neuropathy. No change in visual field deficit has occurred at 11 months follow-up.

Patient 3

A 67-year-old man had a previous history of inferior myocardial infarction and recent development of crescendo angina. Past medical history was remarkable for a transient ischemic attack manifested by brief right-hand clumsiness, which occurred 5 months before operation. Noninvasive studies of the carotid and subclavian arteries performed at that time demonstrated only mild abnormalities of the right external carotid artery.

Cardiac catheterization revealed left main coronary artery disease, and the patient underwent quadruple-vessel coronary artery bypass grafting. On the third day after operation, the patient complained of blurring of vision in the left eye. Ophthalmologic examination revealed a left homonymous hemianopia consistent with a lesion posterior to the optic chiasm. Noninvasive studies suggested plaque in the left carotid artery but no clinically significant stenoses. A computed tomographic scan of the brain revealed a small infarct in the right occipital lobe. An

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echocardiogram of the heart revealed good left ventricular function and no evidence of clot. The patient was given aspirin and dipyridamole after operation and had no further ocular or neurological difficulties. His cardiac condition has been stable for 4 years, but he has a persistent left homonymous hemianopia.

Patient 4

A 67-year-old man had a history of crescendo angina and a positive exercise tolerance test. Physical examination revealed no evidence of carotid bruits. Cardiac catheterization revealed severe triple-vessel coronary disease, and coronary artery bypass grafting was performed.

The patient was somewhat agitated during the first 2 days after operation. Recurrent atrial and ventricular arrhythmias were treated with lidocaine, digoxin, propranolol hydrochloride (Inderal, Ayerst Laboratories, New York), and quinidine. On the third postoperative day, he complained of blurred vision. Ophthalmologic examination revealed a retinal infarct, probably asymptomatic, as well as a left superior homonymous quadrantanopia. Because the patient had arrhythmias, the possibility of an embolus from the heart was considered. An echocardiogram revealed good ventricular contraction and no evidence of a clot. The patient was treated with blood transfusions to raise the hematocrit from 21% to 30%, and anticoagulation was accomplished with sodium warfarin (Coumadin, Du Pont Pharmaceuticals, Wilmington, DE). A computed tomographic scan of the brain revealed a probable right occipital infarct. The patient was discharged from the hospital and was stable for 6 months with no cardiac symptoms and with gradual adjustment to the visual field deficit. He subsequently died of cerebral hemorrhage.

Comment

Neurological complications after cardiopulmonary bypass have numerous potential causes [1, 3, 4, 7, 8]:

- Emboli
  - Cardiopulmonary bypass circuit debris
  - Platelet fibrin emboli
  - Air
  - Fat
  - Left ventricular thrombus
  - Ascending aorta atheroma
  - Valve
    - Vegetation
    - Thrombus
    - Calcium
- Cerebral hypoperfusion
  - Preexisting cerebrovascular disease
  - Hypotension
  - Low flow
  - Hypoxemia
  - Anemia
  - Cannula placement

The effects of these factors may be accentuated by preexisting cerebrovascular disease.

The reported incidence of neurological dysfunction after open heart operations is proportional to the care with which these complications are sought. Some careful prospective studies reveal an overall incidence of neurological complications of 61% to 65% [1, 2] after coronary bypass grafting. However, many of these findings are minor, including drowsiness, peripheral nerve deficits, primitive reflexes, and subtle neuropsychiatric dysfunction. Such complications are usually of minor clinical significance and of limited duration [1, 2, 5, 6, 8]. Serious, clinically evident central nervous system complications resulting in death or major disability occur in 1% to 2.4% of patients [1, 3, 4, 8]. These complications have increased in recent years in proportion to the increasing age of the patient population undergoing open heart operations [4].

Among the most common central nervous system deficits after open heart operations are those involving the eye and the visual pathways. The three most commonly reported vision-threatening complications are those we observed in our series: retinal emboli, occipital infarct, and ischemic optic neuropathy [1, 7–16].

Retinal Emboli

The retina is considered to have "end arteries" with only limited connection between the retinal and choroidal vessels at the disc [17]. The central retinal artery is a branch of the ophthalmic artery, which in turn originates from the carotid artery. Occlusion of the central retinal artery produces painless monocular blindness. Occlusion of only a branch of the artery results in a limited field defect or blurred vision. Ophthalmoscopic examination in such patients reveals a milky white, edematous, pale retina or segment of retina, often with a cherry-red spot at the macula, resulting from visualization of the normal-appearing choroid surrounded by edematous retina [18, 19]. The arteries may appear narrowed, with fragmentation of the blood column.

Early studies of the effects of cardiopulmonary bypass and open heart operations on the retina were undertaken almost two decades ago. Williams [15] performed careful examinations of the fundi in 7 patients before and after they underwent open heart operations. All patients had evidence of microembolization or retinal microinfarction. The emboli were believed to consist of blood elements, platelet-fibrin aggregates, cholesterol, fat, and silicone antifoam [15, 16]. In the prospective study of Gutman and Zegarra [7], 4% of 100 patients who underwent coronary bypass had evidence of focal retinal ischemia, but none had permanent visual loss.

More recent studies have confirmed that retinal microembolization continues to result from open heart operation despite advances in arterial filtration and extracorporeal circulation. In the prospective study by Shaw and co-workers [1] of 312 patients who underwent coronary artery bypass grafting, retinal findings were common, including cotton-wool spots indicative of retinal infarction in 17% of the patients. Half of these patients had symptomatic visual disturbances. Retinal emboli were detectable in 2.6% of patients, half of whom were symptomatic. Breuer and associates [8], in a prospective neurological study of 421 patients who underwent bypass grafting, noted a 5% incidence (24 events in 22 patients) of central nervous system infarction. Approximately one third of these infarctions involved either the optic nerve (2 patients) or retinal vessels (5 patients).

In the most detailed study to date, Blauth and associates [9] performed fluorescein retinal angiography in 21 patients five minutes before termination of cardiopulmonary bypass. Evidence of retinal microvascular occlusion was found in all patients, and cotton-wool spots indicative of local retinal ischemia subsequently developed in 9.5%. Most of these occlusions underwent partial reperfusion within 30 minutes after discontinuation of cardiopulmonary bypass; eight days after operation, only 12.5% of the patients had persistently occluded vessels. No correlation with duration of cardiopulmonary bypass or use of a 40-μm mesh arterial filter was found. Only 1 of 21 patients had a clinically perceptible change in visual acuity, and this was minimal. In concomitant canine experiments, histological studies of the retina after cardiopulmonary bypass revealed 20- to 70-μm platelet–fibrin microaggregates in 78% of the subjects studied [9]. These studies corroborate previous evidence that retinal embolization is common after open heart operations but that it is most often transient and asymptomatic.

Occipital Infarction

Ischemic infarction involving the central visual pathways, particularly the occipital cortex, may produce a homonymous hemianopia [7, 20] unless the injury is bilateral, in which case it may produce "cortical blindness." Specific characteristics of the field defect, such as degree of congruity, may yield further localizing information, which can be corroborated by other physical findings, electroencephalography, and computed tomographic scan of the brain. Such infarctions may result from air or particulate emboli or from generalized hypoperfusion in "watershed" areas.

Taugher [11], in a series of 808 patients undergoing open heart operations, reported 10 patients who experienced visual loss ranging from central and paracentral scotomas to homonymous hemianopia to total cortical blindness. Four of these 10 patients had associated hemiparesis. The cause of the visual loss in each patient, as determined from a brain scan, was occipital cortical infarct. Shaw and associates [1], in their prospective study of 312 patients who underwent bypass grafting, reported an overall rate of cortical stroke of 5%; half of these patients had a visual defect alone or in conjunction with other neurological findings. The defects ranged from quadrant defects and hemianopia to cortical blindness. Russell and Bharucha [10] described 4 patients who sustained bilateral parietal occipital ischemia after cardiac operations, leading to cortical blindness. This was believed to result from generalized cerebral hypoperfusion in the border zone areas between the distributions of the middle and posterior cerebral arteries, not from emboli. Vision improved within 6 weeks, and good visual acuity was regained by all patients, although 1 patient still had a homonymous hemianopia.

Anterior Ischemic Optic Neuropathy

Anterior ischemic optic neuropathy is the least well understood ocular complication of open heart operations. Even in the more common noncardiac surgical presentations, the cause and pathophysiology of anterior ischemic optic neuropathy are controversial. This condition has been reviewed extensively by Hayreh [21] and Miller [22] and is believed to result from interruption of the blood supply to the optic nerve head. The nerve head anterior to the lamina cribrosa and the laminar portions of the nerve head are supplied by branches of the posterior ciliary artery [22]. Ischemia in this distribution leads to infarction of the retrolaminar and laminar portions of the optic nerve. Variable amounts of pial and central retinal artery collaterals may explain why ischemic optic neuropathy develops in some patients and does not under similar circumstances in others [22]. It has also been observed that patients with anterior ischemic optic neuropathy have little or no physiological cupping of the optic disc. This is correlated developmentally with a small scleral canal. Under conditions of mild ischemia and resulting edema, the axons in such patients may be more crowded than in others, further contributing to capillary compression and ischemia [23].

Anterior ischemic optic neuropathy has been observed in patients with hypertension, arteriosclerosis, diabetes, chronic migraine, vascular occlusive disease, and various hematologic disorders [12, 13, 22]. A most interesting and well-known association has been found with blood loss from the gastrointestinal tract or uterus [21]. The optic neuropathy may occur immediately after the event or may be delayed for weeks. The etiology of optic nerve head ischemia in such instances is multifactorial and may include both hypotension and anemia. Hayreh [21] believes that a central unifying element of the pathophysiology is a high circulating level of sympathetic amines. This results in vasoconstriction of the posterior ciliary arteries and of peripapillary choroidal vessels supplying the optic nerve. The vascular effect of these sympathetic amines is enhanced by the absence of an effective blood-optic nerve head barrier. All these factors—anemia, hypotension, and high levels of sympathetic amines—are present in varying degrees in most patients who undergo open heart operations.

Furthermore, in a prospective study of 24 patients, Larkin and associates [24] reported that intraocular pressure increased appreciably, coincident with hemodilution, during cardiopulmonary bypass. These investigators theorized that the combination of increased intraocular pressure and decreased arterial perfusion pressure to the optic nerve head increased the risk of anterior ischemic optic neuropathy. In another more recent prospective study of 46 patients, Deutch and Lewis [25] demonstrated that intraocular pressure in the immediate postoperative period was often appreciably elevated for as long as three days.

Clinically, patients with anterior ischemic optic neuropathy experience sudden painless visual deficit. This varies in severity from a slight decrease in visual acuity to no light perception. The most characteristic visual field defect is an altitudinal scotoma, usually inferior. Arcuate and central scotomas may also occur. Visual acuity within the retained visual field may be normal [22]. Examination of the eye reveals a swollen and, usually, pale disc, which may be associated with retinal hemorrhage or cotton-wool spots. As the acute ischemic insult resolves, optic atrophy is noted. Anterior ischemic optic neuropathy may be bilateral, and the symptoms may appear synchronously or metachronously [22]. The condition generally occurs in patients aged more than 50 years, and both men and women are equally affected. Visual function rarely improves.

Three reports have specifically discussed anterior ischemic optic neuropathy occurring after open heart operations. Sweeney and associates [13] reported 7 patients in whom this complication developed within a 3-year period, which represented 0.1% of the open heart surgery population at their institutions. Ages ranged from 44 to 61 years. All 7 patients noted their symptoms immediately after operation or as soon as they had recovered sufficiently to communicate. Three patients had preexisting diabetes, 3 patients had hypertension, and 4 patients had intraoperative hemorrhage and hypotension. No evidence of arteritis and no evidence of other systemic or retinal emboli were found. Findings of computed tomographic scans of the brain were normal in 5 of the patients, and 1 patient had a coexisting parietal temporal infarct. Sweeney and associates suggested the role of complement-activated vasoconstriction and microcirculatory "sludging" from hypothermia as possible etiological factors. Tice [12] described 3 cases of anterior ischemic optic neuropathy occurring abruptly four to six days after open heart operation in patients who were profoundly anemic (hematocrit, 15% to 20%). These neuropathies apparently resulted in permanent blindness. Tomsak [26] reviewed 2 cases associated with bypass grafting and suggested emboli, including some to the optic nerve itself, as a possible cause of anterior ischemic optic neuropathy.

Prevention

Postoperative visual complications may result from embolization of air or particulate debris, from nonembolic hypoperfusion of the central nervous system, or from ischemia of the optic nerve. Because no satisfactory treatment exists for any of the described forms of visual loss after open heart operation, prevention is essential. Although hypertension, diabetes, hypercholesterolemia, and a history of preexisting cerebrovascular disease would appear to be predisposing factors, many patients who undergo cardiac operation have such conditions. In our experience, we have not been able to identify any common etiological factors.

Reducing the incidence of macroembolization and microembolization requires meticulous attention to surgical technique. The aorta should always be palpated before aortic cannulation to assess the presence of calcium in the wall, particularly if calcium is observed on preoperative chest roentgenography or cardiac catheterization. We use a "no-clamp" technique for aortic cannulation and decannulation, and pump flow is reduced during any subsequent application of clamps to the aorta. In patients with diseased aortas, some soft area for aortic cannulation can usually be identified, although this may necessitate exposure of the transverse arch. When this is not possible, the femoral artery can be cannulated. Some aortas may accommodate a cross-clamp but not a partial occluding clamp, in which case proximal anastomoses are performed with the aorta clamped completely. Manipulation of the most severely diseased ascending aorta may be completely avoided by femoral cannulation, hypothermic fibrillatory arrest without cross-clamping, and multiple internal mammary artery bypass grafts or proximal vein graft anastomoses to the innominate artery.

During valve procedures, meticulous attention must be paid to prevention of particulate embolization. Valves are removed intact when possible, a small amount of suction is maintained in proximity to the diseased valve during excision, and the intracardiac chambers are thoroughly cleansed after valve removal. Air must be removed after any procedure in which a cardiac chamber has been entered; this is facilitated by filling and gently agitating the heart while the anesthesiologist ventilates the lungs to express air from the pulmonary veins. After initial evacuation of air with the aorta clamped, the clamp is released and continuous suction is applied to a vent in the highest portion of the aortic root. The heart is filled and allowed to eject while suction is maintained. In any patient with known left ventricular clot, the heart should be manipulated minimally, and clot extraction may be indicated.

During cardiopulmonary bypass, adequate perfusion flow and pressure, hematocrit, and arterial oxygen and carbon dioxide concentration must be maintained. Our 4 patients underwent 130 to 234 minutes of extracorporeal circulation with a lowest temperature of 25 °C, flow index of 2 to 2.4 $L/m^2/min$, mean perfusion pressure of 52 to 75 mm Hg, and arterial partial pressure of oxygen of 217 to 619 mm Hg. A membrane oxygenator was used in all 4 patients, arterial filtration was used in 2 patients, and a left ventricular vent was used in 1 patient. No problems occurred with the conduct of perfusion in any patient. Although short bypass time and use of arterial filtration might be expected to diminish the total microembolic burden during extracorporeal circulation, these factors do not appear to have a substantial protective effect [9].

Because some evidence exists that endogenous vasoactive amines may contribute to the development of ischemic optic neuropathy [21] and because the production of such substances may be diminished during pulsatile as compared with nonpulsatile cardiopulmonary bypass [27, 28], use of the former mode might theoretically reduce the chance of development of this complication. However, because ischemic optic neuropathy seldom occurs even with nonpulsatile bypass, this would be a nearly impossible hypothesis to substantiate. Therefore, because of the potentially deleterious effects of vasoconstrictor drugs (eg, phenylephrine hydrochloride) not only on optic nerve circulation but elsewhere in the body as well, limiting their use to situations in which systemic vascular resistance and perfusion pressure are substantially decreased appears prudent.

Although every effort should be made to preserve blood and to avoid transfusions, intraoperative or postoperative anemia with a hematocrit less than 20% may be a contributing factor in the development of anterior ischemic optic neuropathy and should be avoided [12].

Finally, the role of intraocular pressure elevation needs to be evaluated further. Prophylactic antiglaucoma medications may have some role in the prevention of ocular complications of open heart operations.

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Hematological Complications With the St. Jude Valve and Reduced-Dose Coumadin

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We examined hematological complications in 415 patients having valve replacement with the St. Jude mechanical prosthesis (212, aortic valve replacement [AVR]; 159, mitral valve replacement [MVR]; and 44, AVR + MVR). There were 164 men and 251 women with a mean age of 59 years (range, 20 to 88 years). Preoperatively 386 patients were in New York Heart Association functional classes III and IV. There were 154 associated procedures (37%), the most common being myocardial revascularization. Overall hospital mortality was 7.5% (31/415), 7% after AVR, 8% after MVR, and 7% after AVR + MVR. All operative survivors were anticoagulated with Coumadin (crystalline warfarin sodium) to maintain the prothrombin time at 1.5 times control. During a mean follow-up of 21 months (range, 6 to 60 months), there were 29 late deaths (7.6%) and 5 patients (1.3%) lost to follow-up. No patient experienced structural valve degeneration. At 48 months, actuarial freedom from thromboembolism was 87% ± 3% after AVR and 91% ± 9% after MVR; from anticoagulation-related hemorrhage, 97% ± 3% after AVR and 91% ± 3% after MVR; and from hemolysis, 100% after AVR and 98% ± 2% after MVR. Freedom from all valve-related morbidity at 4 years was 82% ± 5% after AVR and 75% ± 10% after MVR. Actuarial survival at 48 months was 80% ± 4% after AVR and 65% ± 7% after MVR.

(Ann Thorac Surg 1989;48:280–3)

The hemodynamic performance and durability of the St. Jude mechanical valve are excellent [1–7]. Its primary clinical limitations and those of other mechanical valves derive from interaction of the artificial surfaces with components of blood, particularly the coagulation system. In a review of articles published since 1979, Edmunds [8] noted that approximately 75% of the complications in patients with mechanical valves were related to thromboemboli and bleeding due to anticoagulation. In most studies in which it is documented, the practice when Coumadin (crystalline warfarin sodium) is used is to adjust the dose to maintain the prothrombin time between 1.5 and two times control. Attempts to manage adult patients with St. Jude and other mechanical valves using antiplatelet agents in lieu of Coumadin have not led to acceptable rates of thromboembolic and thrombotic complications [9].

Because of the excellent hemodynamic performance of the St. Jude valve and design considerations thought to reduce the risk of thromboembolism, our patients with the St. Jude valve were managed with reduced Coumadin, the dose adjusted to maintain the prothrombin time at 1.5 times control. We examined all hematological complications in a consecutive series of patients with St. Jude mechanical valves managed in this way between 1983 and 1988.

Material and Methods

St. Jude valve replacements were done in 415 patients at Brigham and Women's Hospital between 1983 and 1988. Isolated aortic valve replacement (AVR) was performed in 212, isolated mitral valve replacement (MVR) in 159, and both AVR and MVR (AVR + MVR) in 44. There were 164 men and 215 women with a mean age of 59 years and an age range of 20 to 88 years. Preoperatively 177 patients were in New York Heart Association functional class IV, 209 were in class III, 28 were in class II, and 1 patient was in class I. An associated procedure was performed in 154 patients (37%), most often myocardial revascularization.

There were 31 early deaths (within 30 days postoperatively), an overall operative mortality of 7.5%. Operative mortality was 7.1% (15 patients) after AVR, 8.2% (13 patients) after MVR, and 6.8% (3 patients) after AVR + MVR. Causes of operative death included myocardial infarction in 11 patients, low cardiac output in 11 patients, arrhythmia in 5 patients, and a variety of other causes in 4 patients.

Operative survivors were anticoagulated with Coumadin to maintain the prothrombin time at 1.5 times control, initially by daily measurement and then weekly or less often once the Coumadin dose was stable after discharge. Each patient was followed and the Coumadin dose adjusted by his or her local physician. No patient was also on a regimen of antiplatelet agents. Follow-up was obtained by direct telephone contact. Any transient neurological event or visual defect was considered a thromboembolic event. All completed strokes and hemorrhages were considered valve related.

Results

During a follow-up that ranged from 6 to 60 months (mean follow-up, 21 months), there were 29 late deaths (7.6%) and 5 patients (1.3%) were lost to follow-up.

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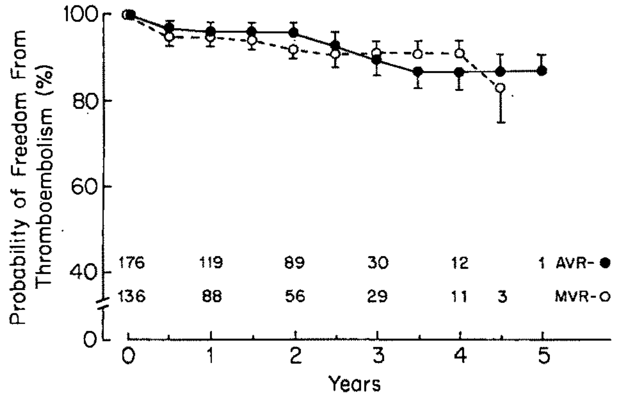

Fig 1. Actuarial probability of freedom from thromboembolism. Numbers in each group represent patients at risk. (AVR = *aortic valve replacement;* MVR = *mitral valve replacement.)*

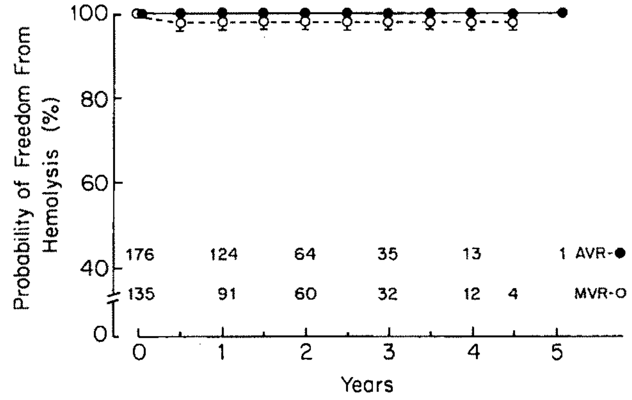

Fig 3. Actuarial probability of freedom from hemolysis. Numbers in each group represent patients at risk. (AVR = *aortic valve replacement;* MVR = *mitral valve replacement.)*

Causes of late death were as follows: cardiac-related in 15 patients, hemorrhage in 5, stroke in 2, and other nonvalve-related in 7. Three hundred twenty-two survivors were in New York Heart Association functional class I or II. Structural valve degeneration occurred in no patient, but there were four cases of prosthetic valve endocarditis, three after AVR and one after AVR + MVR. Five patients, 1 after AVR and 4 after MVR, had documented perivalvular leak.

Actuarial probabilities of freedom from a variety of hematological complications were calculated at 48 months of follow-up for patients who underwent AVR or MVR. The probability of freedom from thromboembolism was 87% ± 3% after AVR; this complication occurred in 11 patients. Similarly, 11 thromboembolic events occurred in patients after MVR, and the actuarial probability of freedom from this complication was 91% ± 9% (Fig 1). Two of these thromboembolic events caused fatal strokes. There was one instance of valve thrombosis after MVR. Because of pregnancy, this patient had been told to discontinue Coumadin.

The probability of freedom from anticoagulation-related hemorrhage at 4 years was 97% ± 3% after AVR (one event) and 91% ± 3% after MVR (five events) (Fig 2). Five of the events were fatal.

There was no incidence of hemolysis after AVR (actuarial probability of freedom from this complication, 100%). Hemolysis was defined as reticulocytosis and transfusion requirement without defined bleeding and was seen in only 3 patients with perivalvular leak after MVR. The probability of freedom from this complication after MVR was 98% ± 2% at 4 years (Fig 3).

The probability of freedom from all valve-related morbidity including infection and perivalvular leak at 4 years was 82% ± 5% after AVR and 75% ± 10% after MVR (Fig 4). Actuarial survival at 48 months was 80% ± 4% after AVR and 65% ± 7% after MVR (Fig 5).

After AVR + MVR, only one nonfatal thromboembolic event was documented. No instances of anticoagulant-related hemorrhage occurred.

Comment

The excellent hemodynamic performance and freedom from structural valve degeneration of the St. Jude mechanical prosthesis have been well documented in other

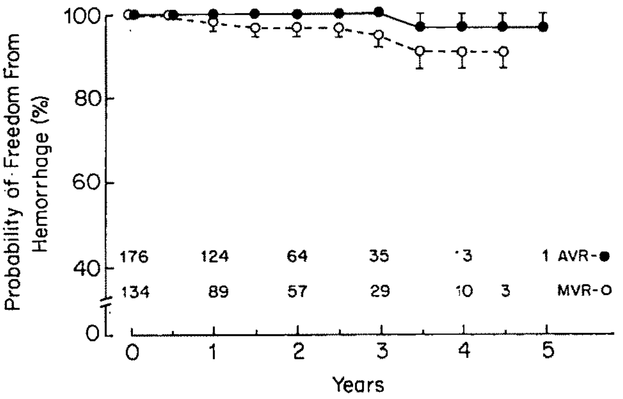

Fig 2. Actuarial probability of freedom from anticoagulant-related hemorrhage. Numbers in each group represent patients at risk. (AVR = *aortic valve replacement;* MVR = *mitral valve replacement.)*

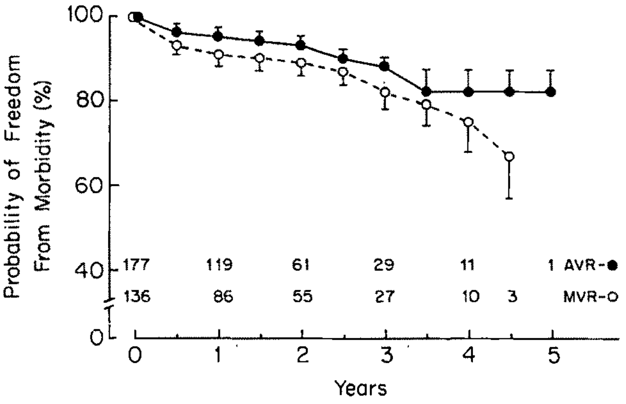

Fig 4. Actuarial probability of freedom from all valve-related morbidity. Numbers in each group represent patients at risk. (AVR = *aortic valve replacement;* MVR = *mitral valve replacement.)*

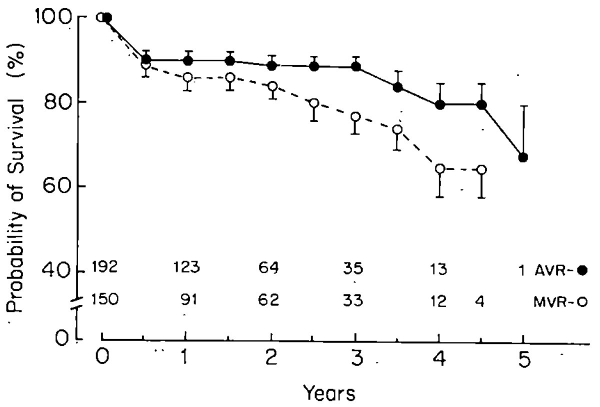

Fig 5. Actuarial probability of survival. Numbers in each group represent patients at risk. (AVR *= aortic valve replacement;* MVR *= mitral valve replacement.)*

studies [1–7] and are confirmed by the experience reported here. Interaction of the mechanical valve surfaces with the components of the coagulation system leading to thromboembolic complications and mandatory use of anticoagulants leading to hemorrhagic complications remain the principal limitations of these prostheses. Despite efforts to manage patients without Coumadin anticoagulation, in adult patients, at least, rates of thromboembolism and valve thrombosis have been unacceptably high when antiplatelet agents alone have been used [5, 9, 10]. In our experience, reduced Coumadin dose adjusted so that the prothrombin time is 1.5 times control is associated with excellent clinical performance and acceptable rates of thromboembolic and hemorrhagic complications. These continue to be major causes of morbidity and mortality, however.

The correct dose of an anticoagulant after prosthetic valve replacement has been derived empirically after years of experience with patients who have these valves. Previous practice had been to adjust anticoagulation to maintain the prothrombin time at greater than 1.5 times but usually less than two times control value [8, 11–14]. Even at these levels, thromboembolic events remain a critical problem after valve replacement with older mechanical prostheses. Furthermore, hemorrhagic complications are not unusual. In our experience [15, 16] with tilting-disc valves and Coumadin anticoagulation to prothrombin times twice normal, freedom from thromboemboli was 80% and from hemorrhage, 90% at 9 years. In the review of the Starr-Edwards caged-ball valve by Miller and associates [17], the 5-year probability of freedom from thromboemboli and hemorrhage was 62% and 82%, respectively. An inverse relationship between thromboembolism and hemorrhage has also been documented with the caged-ball prosthesis [18]. Comparing patients managed between 1960 and 1972 with those seen between 1973 and 1980, decreased rates of thromboembolism were achieved at the expense of increased rates of anticoagulant-related bleeding.

Newer prostheses such as the St. Jude valve incorporate improved material and design features that enhance hemodynamic performance and reduce thrombogenicity. Central-flow characteristics, pyrolytic carbon construction, and improved hinge design have made the St. Jude valve a standard by which to judge new designs. Because of these features, we have successfully managed the patients presented here using a reduced dose of Coumadin. Although valve thrombosis and structural valve degeneration have been observed with the St. Jude valve [19, 20], to date we have seen only one instance of valve thrombosis in our patients managed in this way.

Our experience with a low incidence of thromboembolism, anticoagulant-related hemorrhage, and hemolysis with the St. Jude valve in patients treated with Coumadin at a reduced dose over 5 years has been encouraging. However, challenges remain and must be addressed by development of better understanding of the interaction of these prostheses with all components of blood, particularly the coagulation system. Only when problems related to this interaction are solved will durable valve replacement devices with both excellent hemodynamic performance and low rates of thrombogenicity without anticoagulation be available for patients in need of valve replacement.

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REVIEW OF RECENT BOOKS

Socioeconomics of Surgery

Edited by Ira M. Rutkow
Philadelphia, C.V. Mosby, 1989
423 pp, illustrated

Reviewed by Benson B. Roe, MD

This comprehensive text of 423 pages presents a studiously documented review of the current factors associated with the timely issue of surgical economics, which nearly all surgeons recognize to be in the throes of transition. The thrust of this study can best be summarized in the author's words: "The transformation of United States' health care from a 'cottage industry' to a mammoth government-industrial-medicine complex is undeniable. To the surgical profession, the central question must be how it views itself relative to this change and where it fits into the rapidly changing system."

Because of this rapid flux the book is probably destined to become out of date almost as the ink dries. Nevertheless it represents an extremely valuable resource and background for all who are involved in the transition process. Its wide variety of individual viewpoints is supplemented by an exhaustive review of the current literature in which conflicting views are expressed and from which a prodigious amount of data was extracted to illustrate the issues in question.

The book is segmented into five parts: Surgical Demographics, Delivery and Financing of Surgical Services, Quality of Surgical Care, Legal and Ethical Issues, and Summary. Each of the 24 chapters is authored by one or more distinguished experts on the subject (including several of those actively involved in the current legislative and administrative proceedings on physician remuneration), adding to the comprehensive and authoritative character of the work.

Notwithstanding the overall excellence of the book, I found a few key elements to be missing. The authors' devotion to objective information resulted in side-stepping the highly charged emotional aspects of physician autonomy, self evaluation, and rationalized greed. These important feelings play an unmistakable role in socioeconomic behavior patterns, yet the studies suggest that actions are the result of rational decisions. Although the traditional image of a physician as unselfish, dedicated, and completely honest may still be widely applicable, I believe that it is no longer a generality that can be reliably applied to economic policy.

The authors carefully provide the explanations and refutations for the problems of unnecessary operations, variations in charges, and assessment of severity with minimal recognition of the incentives for greed in the system.

The capriciousness of many surgical charges, as manifested by their frequent lack of correlation with relative risk, skill, experience, results, or cost of practice, warrants more attention. Nor do the authors give more than passing reference to the substantial economic impact of duplicated charges in the form of "unbundling" and overlapping responsibility.

In the chapter on surgical decision making, Dr Clarke ignores the powerful market role of the referring physician whose desires may prevail over contrary surgical judgement by conditioning his referral choices to surgeons who will comply to "get the business."

Notwithstanding these deficiencies—which may be exaggerated in the eyes of this reviewer—the book is a valuable and monumental rendition of a very important issue to all surgeons and to the economy at large. It is required reading for all who toil in that field and recommended reading for all practicing surgeons.

San Francisco, California

Chest Wall Implantation of Lung Cancer After Thin-Needle Aspiration Biopsy

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Department of Surgery, Walter Reed Army Medical Center, Washington, DC, and the Uniformed Services University of the Health Sciences, Bethesda, Maryland

Percutaneous aspirational biopsy of intrathoracic lesions has become a popular technique. One of the rarest complications is that of implantation of malignant cells within the needle tract and subsequent development of a chest wall mass. A case of chest wall implantation of adenocarcinoma of the lung after thin-needle biopsy is reported. The lesion was successfully treated with radical full-thickness excision of the chest wall and immediate reconstruction with a large rectus abdominis musculocutaneous flap.

(Ann Thorac Surg 1989;48:284–6)

Percutaneous aspirational biopsy has become a popular technique in the diagnosis of certain pulmonary densities. Although controversial, especially for operable lesions, the indication is usually to confirm a suspected malignancy when confronted with a newly discovered peripheral lesion or one that has exhibited increased size [1]. One of the rarest complications is that of implantation of malignant cells within the needle tract and subsequent development of a chest wall mass. Of the few reported cases, most have been associated with the Vim-Silverman cutting needle [2–4]. There have been, to our knowledge, no reports of adenocarcinoma implantation after thin-needle biopsy (18 to 23 gauge). Likewise, although several reports describe the implant metastasis, none have addressed the issue of how such a lesion should be treated, especially if the mass is fixed to the chest wall. We report a case of thin-needle implantation of pulmonary adenocarcinoma and its management by aggressive chest wall resection and flap reconstruction.

A 46-year-old woman was referred for evaluation of a nonhealing skin lesion over the right anterior chest wall of 4 months' duration. Six months previously, the patient had undergone a right upper lobectomy for a large adenocarcinoma (T2 N0 M0) of the lung. Subsequently, she received no chemotherapy or radiotherapy, was free of detectable disease, and led an active lifestyle. Significantly, the chest wall nodule was located far from the thoracotomy incision and exactly where a diagnostic thin-needle (18-gauge Lee needle) biopsy had been performed before the lobectomy. The ulcer measured 8 mm in diameter and was associated with a 3 × 2-cm fixed, nontender, firm mass over the right prepectoral region (Fig 1). Incisional biopsy of the lesion showed moderately well-differentiated adenocarcinoma that correlated closely with the original tumor (Figs 2, 3). Computed tomographic scanning indicated deep involvement of the chest wall in the same direction as the original needle aspiration (Fig 4).

A wide, full-thickness excision of the chest wall was performed and a small portion of adherent lung was also removed to ensure en bloc resection. Random histological frozen sections at the margins were free of tumor, and examination of the specimen showed extension deep into the muscle layer. The surgical defect measured 15 × 12 cm and encompassed the second, third, and fourth ribs as well as the right hemisternum. A large contralateral rectus abdominis musculocutaneous flap was mobilized, based on the remaining internal mammary artery, and was transposed into the defect. The abdominal and chest

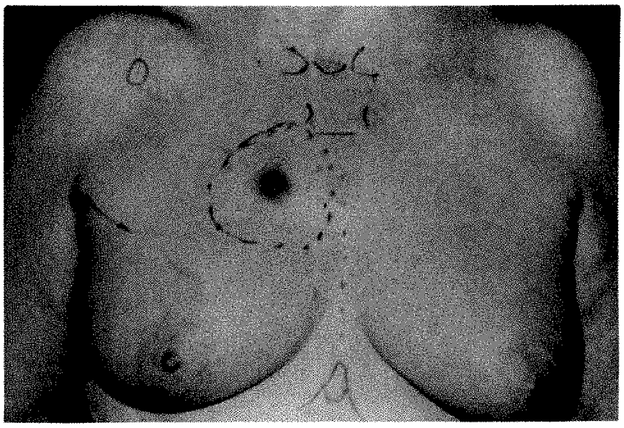

Fig 1. This 46-year-old woman was referred for treatment of an enlarging mass and ulceration on the chest wall. The dashed lines *indicate the palpable borders of the underlying, fixed mass.*

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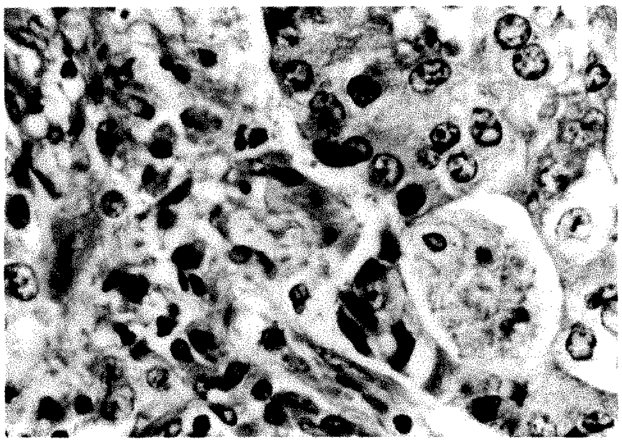

Fig 2. Microscopic section of the original lung tumor showing clusters of adenocarcinoma cells. (Hematoxylin and eosin, ×600 before 50% reduction.)

incisions were closed. The patient was ambulant the following day, the chest tubes were removed within 72 hours, and she was discharged in the first postoperative week. Permanent histology showed adenocarcinoma as noted before, and all margins were clear.

Five months later, clinical suspicion of axillary adenopathy developed. Subsequent axillary dissection showed that one of four nodes contained adenocarcinoma. The patient recovered uneventfully and continues to do well 9 months after her chest wall resection. She continues to show no evidence of residual disease at 15 months after the lobectomy and 9 months after the chest wall resection (Fig 5).

Comment

Although percutaneous needle biopsy was first described in 1883, it was not until the late 1940s that it began to be used regularly as a diagnostic tool in the US. Even then, concerns were raised by Oschner and DeBakey about the risk of needle tract metastasis [5]. Interestingly, in experimental models it has been shown that up to 90% of needle tracts contain malignant cells, yet they carry only a slight risk of developing into frank metastases in the surrounding tissue [6, 7]. Fortunately, the incidence of clinically apparent needle tract metastases is small, with most series reporting less than a 1% occurrence [1, 8].

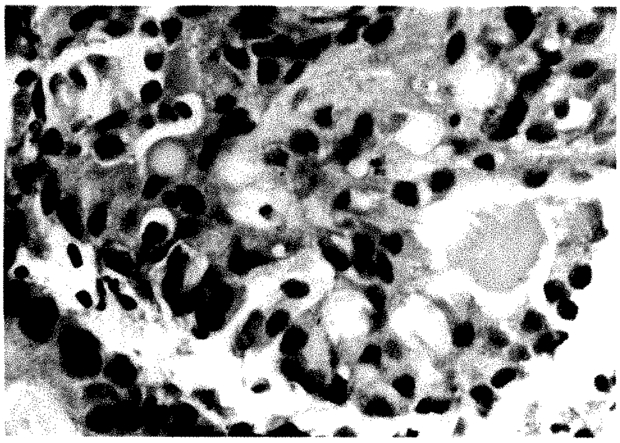

Fig 3. Microscopic section of the implanted chest wall metastasis depicting mucin-containing adenocarcinoma cells seen in the original lesion (see Fig 2). (Hematoxylin and eosin, ×600 before 50% reduction.)

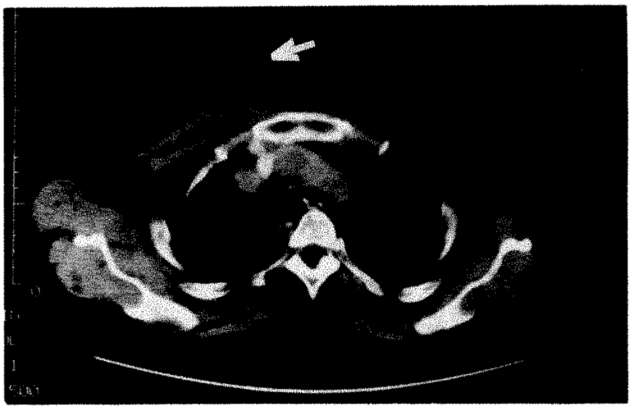

Fig 4. This computed tomographic scan shows a superficial soft tissue density (arrow) at the former biopsy site that extends to the musculoskeletal layer.

Although several cases of needle tract implantation with adenocarcinoma of the lung have been reported, all have occurred with the use of a large-bore Vim-Silverman cutting needle [2–4]. Metastases that have occurred with a thin needle (18 to 23 gauge) have all been of bronchogenic origin [9, 10].

In 1972, Berger and associates [11] raised much controversy when they reported 2 cases of seeding of the pleural

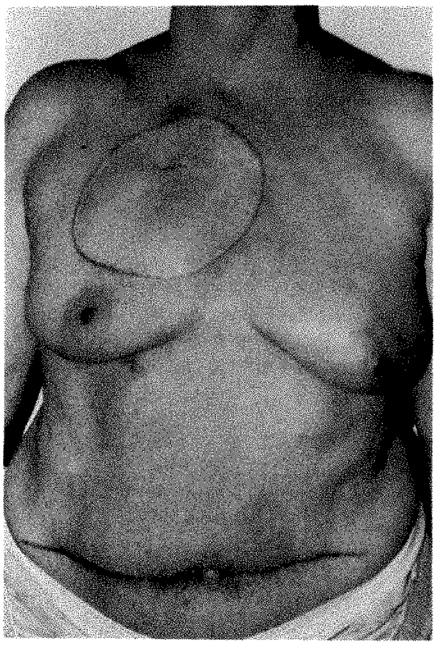

Fig 5. The patient is shown 4 months after chest wall resection and flap reconstruction. She continues to do well 9 months postoperatively and 15 months after right upper lobectomy.

space with squamous cell carcinoma associated with needle biopsy. It was proposed that operable lesions may therefore carry a worse prognosis if needle-biopsied. Two other groups argued that technical difficulties and problems in confirming the nature of the cells within the pleural fluid militated against changing the criteria under which a needle biopsy should be performed [12, 13]. Currently, diagnostic needle biopsy is commonly used with few contraindications.

It is noteworthy that in the present case, not only did the needle biopsy result in soft-tissue extension of the tumor, but the metastasis itself then spread to the axillary nodes.

It is our impression that when a needle-tract metastasis is fixed to the musculoskeletal layer, and if the patient's overall condition is favorable, wide full-thickness chest wall ablation and immediate reconstruction is the treatment of choice, either for cure or for palliation. With currently available methods, this can be accomplished safely in one operation, thereby minimizing hospitalization and cost. When properly selected, durable soft-tissue flaps from the adjacent torso can provide excellent restoration of function with minimal morbidity [14]. In the present case, the rectus abdominis musculocutaneous flap was utilized to meet these requirements. If the lesion is located within an irradiated field, other flap alternatives may also be appropriate [15].

In our series, loss of muscular or musculocutaneous flaps, as well as revision of any flap, has been less than 1%. Likewise, the mortality in major chest wall ablations with immediate reconstruction has been less than 1% [16]. Hence, an aggressive approach to chest wall implants is warranted.

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Malignant Melanoma Metastatic to the Esophagus

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A rare case of metastatic malignant melanoma of the esophagus 11 years after wide excision of a cutaneous malignant melanoma is presented and the relevant literature reviewed. Symptomatic esophageal metastasis is unusual in malignant melanoma. Although the eventual outlook is poor in such cases, worthwhile palliation can be achieved by prompt diagnosis and treatment.

(Ann Thorac Surg 1989;48:287–8)

Malignant melanoma of the esophagus is a rare disease, accounting for only 0.1% of primary esophageal malignant neoplasms [1]. More than a hundred cases of primary malignant melanoma of the esophagus have been reported [2]. Metastatic involvement of the esophagus was first reported in a postmortem study in 1895 [3]. Since then, 6 cases of metastatic malignant melanoma of the esophagus detected clinically have been reported [4–8], although it has been found in up to 4% of postmortem studies of malignant melanoma metastatic to the gastrointestinal tract [9]. We report a case of symptomatic metastatic malignant melanoma of the esophagus.

A 44-year-old woman was seen in July 1987 with a 4-month history of progressive dysphagia and odynophagia. By the time she was seen, she had lost 6 kg. In 1976 she had a 1-cm malignant melanoma excised from her lower lumbar region. Histology of the widely excised specimen showed malignant melanoma confined to the epidermis and upper part of the dermis with a good deal of lymphocytic infiltrate and sparse mitosis. The excision was believed to be complete. In 1980 and 1985, she had two further swellings removed from her lumbar scar, with no evidence of recurrence of melanoma.

Physical findings, laboratory results, chest roentgenogram, abdominal ultrasonic scan, and isotopic scan of bones were all within normal limits. Barium swallow (Fig 1) showed an irregular filling defect in the midesophagus just inferior to the carina. Esophagoscopy showed a polypoid tumor 27 cm from the incisors. Examination of the biopsy specimen showed malignant melanoma. Bronchoscopy performed at the same time showed normal trachea, carina, and bronchial trees.

The patient underwent Ivor Lewis esophagectomy and esophagogastrostomy. There was no evidence of hepatic or intrathoracic metastases at operation. The patient was discharged from the hospital on postoperative day 12 after an uneventful recovery.

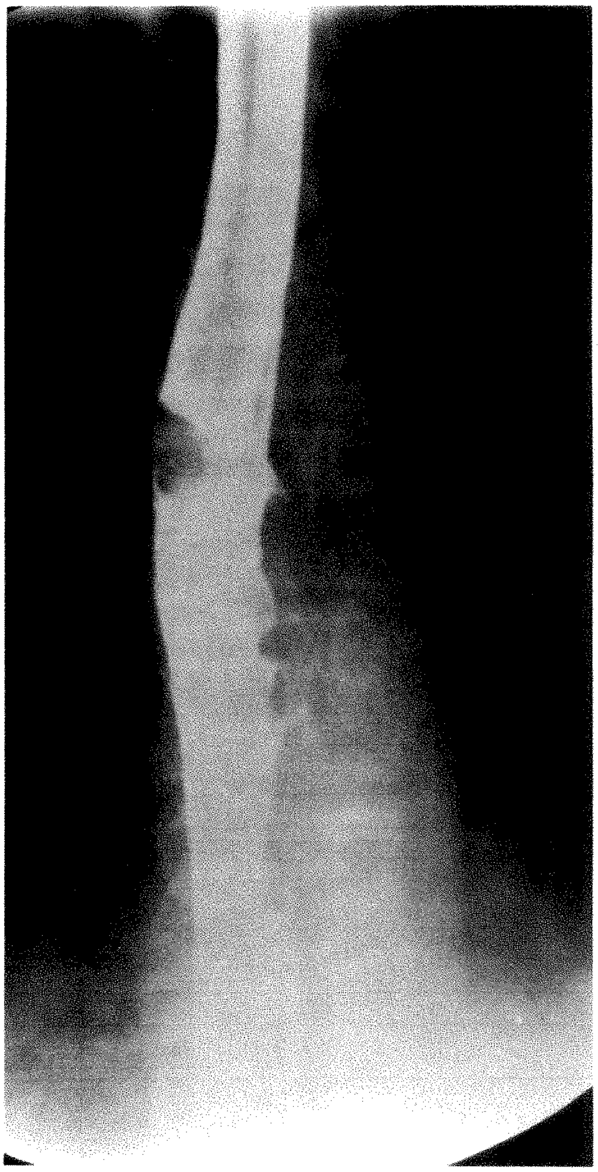

Fig 1. Barium swallow showing irregular polypoid filling defect in the midesophagus.

The resected specimen (Fig 2) contained a polypoid, pigmented lesion of the midesophagus. Microscopic examination of the specimen revealed typical malignant melanoma without junctional activity. The adjacent epithelium showed no evidence of nevus cells or in situ melanoma. A diagnosis of metastatic malignant melanoma of the esophagus was made.

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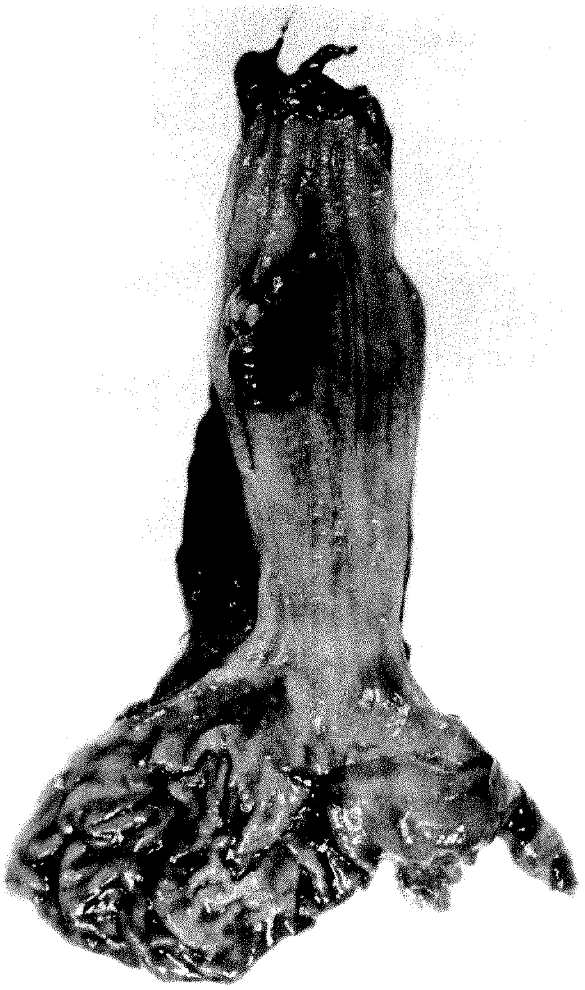

Fig 2. Operative specimen showing polypoid, pigmented lesion of the midesophagus.

At follow-up 6 months after discharge, the patient was found to have disseminated disease, confirmed on excisional biopsy of a left axillary lymph node. The patient died 2 months later; permission for postmortem examination was refused.

Comment

Controversy surrounded the discussion of the existence of primary malignant melanoma of the esophagus until 1962 when melanoblasts were detected in the esophagus in some patients [10]. Malignant melanoma has been reported in an esophagus associated with melanosis of the entire esophagus. In 1949, Allen and Spitz [11] established the criteria for the diagnosis of metastatic, as opposed to primary, malignant melanoma and emphasized the importance of junctional change of the overlying epithelium. There was no evidence of such change in our patient, confirming the metastatic nature of the disease. This correlated well with the previous cutaneous malignant melanoma removed from her back.

Malignant melanoma has the propensity to cause widespread metastatic disease even years after the original treatment of cutaneous lesions. The gastrointestinal tract is a frequent site for such metastases, which are usually multiple [9]. Review of the published studies shows that in the case of the esophagus, primary malignant melanoma appears to be much more common than metastatic malignant melanoma.

Multiple-organ metastases are present in up to 95% of patients with advanced metastatic malignant melanoma. Single-organ metastasis is uncommon. We did not find any evidence of further disease in our patient either preoperatively or at operation. Unfortunately, she had widespread metastases within 6 months of discharge from the hospital.

The outlook of malignant melanoma of the esophagus is generally poor, with survival in most cases of less than a year from diagnosis. Metastatic malignant melanoma appears to carry a similarly dismal prognosis. However, in relatively young and healthy patients, surgical resection would be the method of choice to provide a more satisfactory palliation, until more effective treatment options become available. This may include intralesional α-interferon therapy.

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Long-Term Survival After Triple-Valve Replacement

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A 29-year-old man with rheumatic stenosis and insufficiency of the aortic, mitral, and tricuspid valves underwent urgent triple-valve replacement on January 12, 1966, because of uncontrollable congestive heart failure. Twenty-two years and 8 months later (September 13, 1988) reoperation was necessary to replace the Kay-Shiley tricuspid prosthesis because of progressive stenosis of the valve due to pannus formation. The aortic and mitral prostheses continue to function normally. The patient has again returned to full activity.

(Ann Thorac Surg 1989;48:289–91)

The need to replace the aortic, mitral, and tricuspid valves, a procedure first performed successfully by Starr, is uncommon as repair of one or more of the valves is usually possible. We describe a patient who was successfully reoperated on 22 years and 8 months after triple-valve replacement using three different prosthetic valves. We hope this unique case will be of interest to others.

A 29-year-old man had been managed medically for 3 years for his rheumatic valvular heart disease with catheterization documentation of stenosis and insufficiency of the aortic, mitral, and tricuspid valves. Refractory congestive heart failure eventually developed (Fig 1) and he underwent urgent triple-valve replacement on January 12, 1966.

The aortic and mitral valves had typical calcific and fibrotic changes, and the tricuspid valve was fibrotic without identifiable commissures. The papillary muscles and subvalvular apparatus were excised along with the mitral and tricuspid valve leaflets. The base of the calcific aortic valve leaflets was debrided to provide an acceptable annulus for valve placement.

Three different prostheses were implanted: a Magovern sutureless valve in the aortic position, a Starr-Edwards (model 6120) in the mitral position, and a Kay-Shiley in the tricuspid position (Fig 2). Myocardial protection was provided by modest total body hypothermia of 30°C and continuous cannula perfusion of the left coronary artery with intermittent perfusion of the right coronary artery with blood from the pump circuit. No potassium cardioplegia was used.

Despite a lengthy bypass time, the heart restarted promptly in normal sinus rhythm. No inotropic drugs were necessary at any time postoperatively, and the patient recovered from operation without complications.

Throughout the years he remained physically active with minimal limitation. In 1976 he developed episodes of bradycardia due to sick sinus syndrome. A permanent pacemaker was inserted transthoracically because of the tricuspid prosthesis, and he again continued to do well.

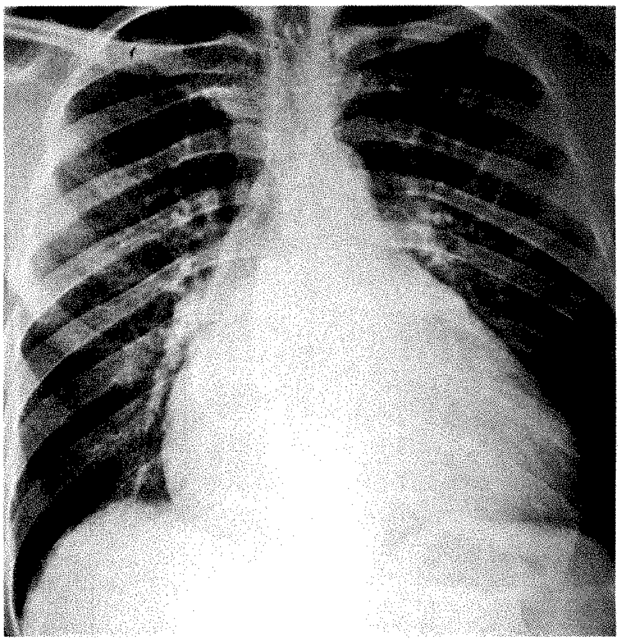

Fig 1. Posteroanterior chest roentgenogram shows marked cardiomegaly of all chambers and congestive heart failure.

Early in 1988 he began to develop signs and symptoms of right-sided failure with ascites and peripheral edema. Cardiac evaluation revealed normally functioning aortic and mitral prostheses, but severe stenosis of the Kay-Shiley tricuspid valve.

On September 13, 1988, at reoperation, marked pannus formation was found on an otherwise normal-appearing prosthesis (Fig 3). There was no disc wear detectable. A Carpentier-Edwards porcine valve (No. 33) was inserted without difficulty. An atrial septotomy was performed and the Starr-Edwards mitral valve was inspected. No abnormalities were seen. The patient recovered unevent-

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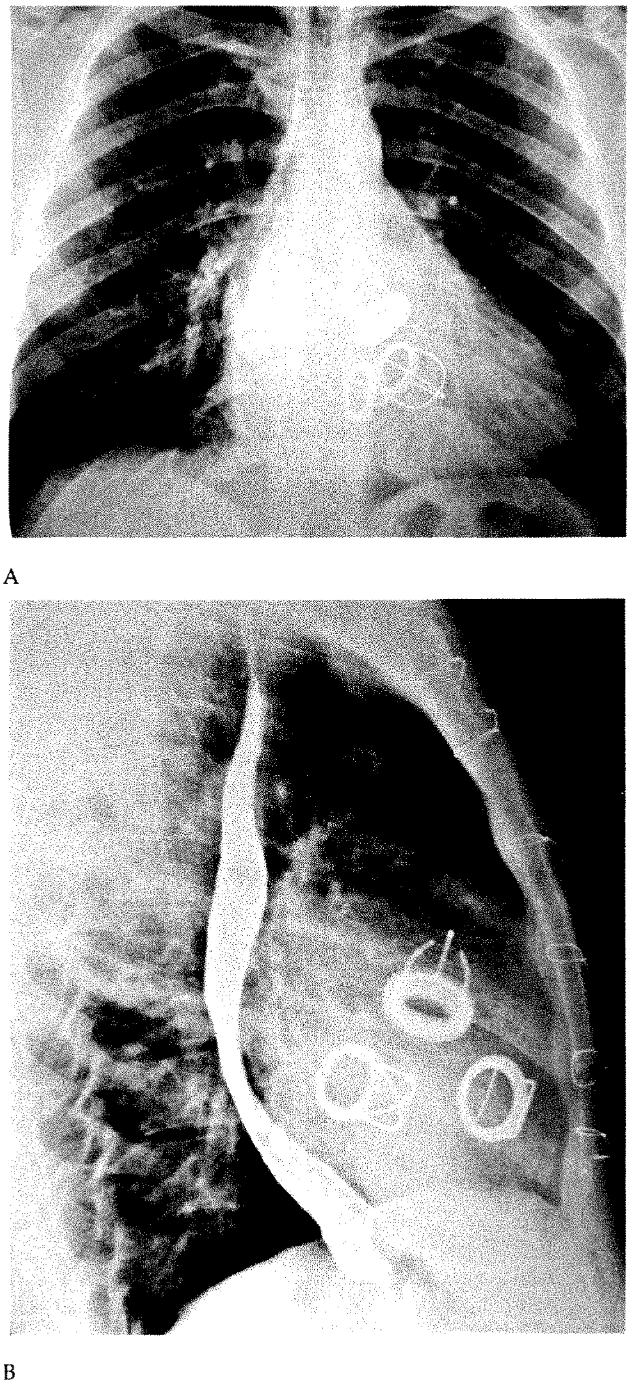

Fig 2. On the posteroanterior (A) and lateral (B) chest roentgenograms the three different valve prostheses can be seen: a Magovern aortic, a Starr-Edwards mitral, and a Kay-Shiley tricuspid.

fully and his failure signs and symptoms have resolved (Fig 4).

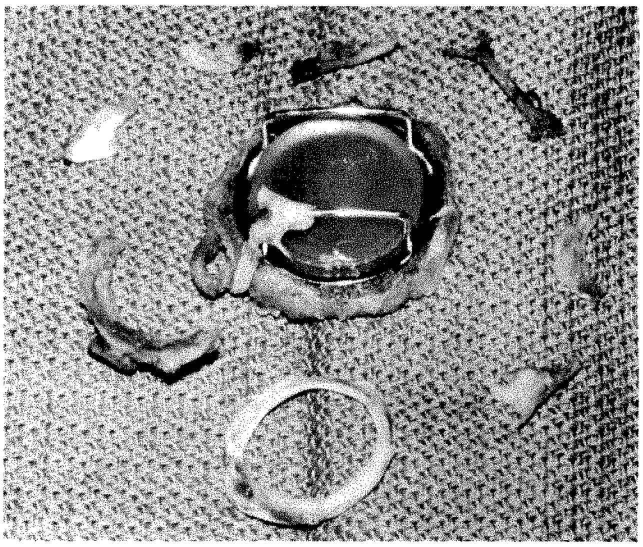

Fig 3. The excised Kay-Shiley valve is structurally intact with no serious disc wear. Progressive stenosis was caused by pannus formation on the inflow surface of the tricuspid prosthesis.

Comment

There are several unusual and perhaps unique features about this case that are worth noting. All three valves were irreparably damaged by the rheumatic process and required replacement. Three different valves were used for the following reasons: (1) a sutureless Magovern valve [1] was used in the aortic position to minimize bypass time. Because of the multiple-point fixation into the aortic annulus by extrudable metallic pins activated by a few twists of the seating device, the valve could be securely inserted much more quickly than the conventional interrupted suture technique used for other valves. (2) The Starr-Edwards valve was used in the mitral position because it was the prosthesis most widely accepted as the best valve available [2]. (3) A Kay-Shiley disc prosthesis [3] was selected for the tricuspid valve replacement because of its very low profile. There was the concern that the more bulky ball and cage of a Starr-Edwards valve might be traumatic to the septum and free wall of the right

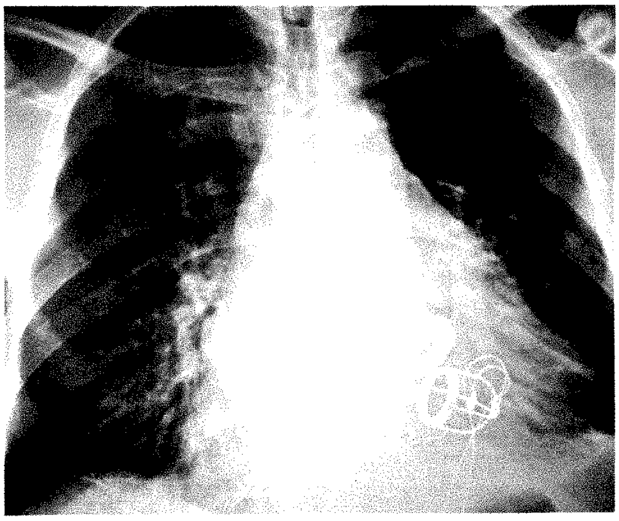

Fig 4. On the posteroanterior chest roentgenogram 10 days after operation, a Carpentier-Edwards tissue valve can now be seen in the tricuspid position, as well as the previously placed pacing wires.

ventricle, and possibly somewhat obstructive as well to right ventricular outflow.

The long-term survival of this patient was especially gratifying because this young man was able to live an active life, and was fortunate enough to avoid any major complications. He had no episodes of endocarditis, thromboembolic events, major hemorrhage, or valve disruption. The very late pannus formation on the valve skirt is a known potential complication of other valves as well, and is not a valve-related mechanical malfunction.

There are few reports of long-term follow-up of survivors of triple-valve replacement. In 1978, MacManus and associates reviewed a 14-year experience with 48 triple-valve replacements [4]. There were nine operative deaths and 21 late deaths, with 43% of the late deaths being valve-related. In 13 of the 17 survivors (mean follow-up, 10.3 years), the functional class was improved over the preoperative status in all but 3. There were, however, 18 patients who experienced 31 embolic episodes of which four were fatal. In addition, 8 operative survivors (20.5%) required re-replacement of a total of 12 (five aortic, three mitral, four tricuspid) prosthetic valves. All mitral and tricuspid valves were re-replaced for thrombotic stenosis of the prosthesis. One of the tricuspid valves was a caged disc prosthesis similar to the one used in our patient.

In 1985, Gersh and co-workers [5] reported the Mayo Clinic experience with 91 patients who had undergone triple-valve replacement. There were 22 perioperative deaths (24%) and 40 late deaths over a median follow-up period of 7.5 years (range, 6 weeks to 20 years). Cumulative survival was 64% at 1 year, 55% at 5 years, 40% at 10 years, and 25% at 15 years. Eight patients required reoperation for prosthetic valve dysfunction. Isolated tricuspid valve malfunction requiring reoperation developed in 2 patients with Starr-Edwards prostheses and in 1 patient with a Björk-Shiley prosthesis. Twelve patients required permanent pacemakers.

The durability of prosthetic valves when compared with tissue valves has been a major advantage for their use. The remarkable performance and structural integrity of these three valves of different types that were used in this patient can be better appreciated by estimating the number of valve actions that have occurred since implantation. Assuming 80 beats/minute over the preceding 22 years and 8 months, then each valve would have opened and closed 953,625,600 times. The life expectancy of the two original valves (Magovern and Starr) that continue to function normally cannot be predicted, but few would challenge the fact that they have fulfilled the claim of durability.

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Laryngotracheoesophageal Cleft: Endoscopic Diagnosis and Surgical Repair

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The laryngotracheoesophageal cleft results from congenital nonfusion of the upper tracheoesophageal septum and cricoid primordium. The diagnosis remains an endoscopic one and often is difficult to make in the neonate. This article describes a method for determining the diagnosis, as well as details of a successful surgical repair.

(Ann Thorac Surg 1989;48:292–4)

Laryngotracheoesophageal (LTE) cleft is an extremely rare congenital anomaly, and the diagnosis is often difficult to make, especially for the unsuspecting examiner. Without early identification and surgical correction, a very poor prognosis exists. This report describes the diagnosis and detailed surgical repair of a neonate with a complex upper LTE cleft.

Endoscopic Diagnosis

An intubated 2,325-g female infant was referred for respiratory distress two days after delivery. She had been intubated because of chest wall retractions and progressive cyanosis. Radiographic studies showed aspiration of contrast material with no anatomical detail being elucidated. On admission, the child was examined with a Storz lens-rod infant bronchoscope, 4.0 mm in outer diameter, which provided adequate ventilation and thorough visual inspection. Just past the epiglottis, a wide posterior laryngeal defect and large esophageal opening was noted. The origin of the esophagus appeared much larger than that of a standard tracheoesophageal fistula. As seen in Figure 1, an H-shaped common pouch was seen with the anterior opening representing the more anterior trachea and the posterior orifice, the esophagus. The crossbridge of the H appeared as the incomplete tracheoesophageal septum. The lower trachea and distal bronchial tree were found to be normal.

Subsequently, the child was reintubated and underwent esophagoscopy to rule out other abnormalities. A 4F Fogarty catheter was introduced into the distal esophagus and the endoscope was removed. Repeat bronchoscopy showed the catheter posterior, creating a groove dorsal to the incomplete cricoid ring, running along the posterior larynx, and entering the esophagus behind the incomplete septum. This maneuver helped confirm the diagnosis of a high LTE cleft that ended at the second tracheal ring.

Surgical Repair

The infant was ventilated and treated with antibiotics until pulmonary infiltrates cleared five days later. During the repair, care was taken not to dislodge the endotracheal tube into the large esophageal opening. A J-shaped incision was made longitudinally just anterior to the left sternomastoid muscle (Fig 2). Using blunt dissection, the strap muscles were retracted anteriorly to allow entrance into the pharynx posterior and lateral to the primordium of the tracheoesophageal septum. This approach allowed protection of the recurrent laryngeal nerve.

The pharyngeal pouch was opened by incising the inferior constrictor muscle longitudinally. In the common pouch the caudal aspect and lateral ridges of the septum were defined and the edges were denuded of mucosa (Fig

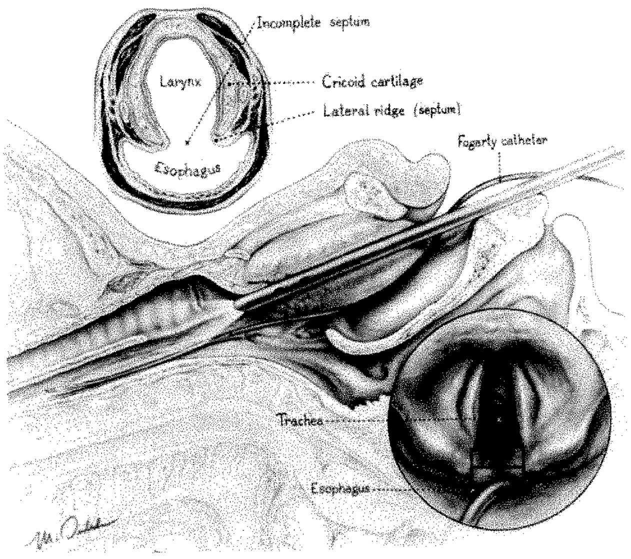

Fig 1. Bronchoscopic diagnosis of a laryngotracheoesophageal cleft, facilitated by passing a 4F Fogarty catheter into the esophageal opening previously. (Upper inset) A cross-section of the most cephalic part of the cleft, showing the deficient cricoid cartilage and septum. (Lower inset) An endoscopic view of the cleft. The crossbar of the H represents the cleft with catheter passing posteriorly.

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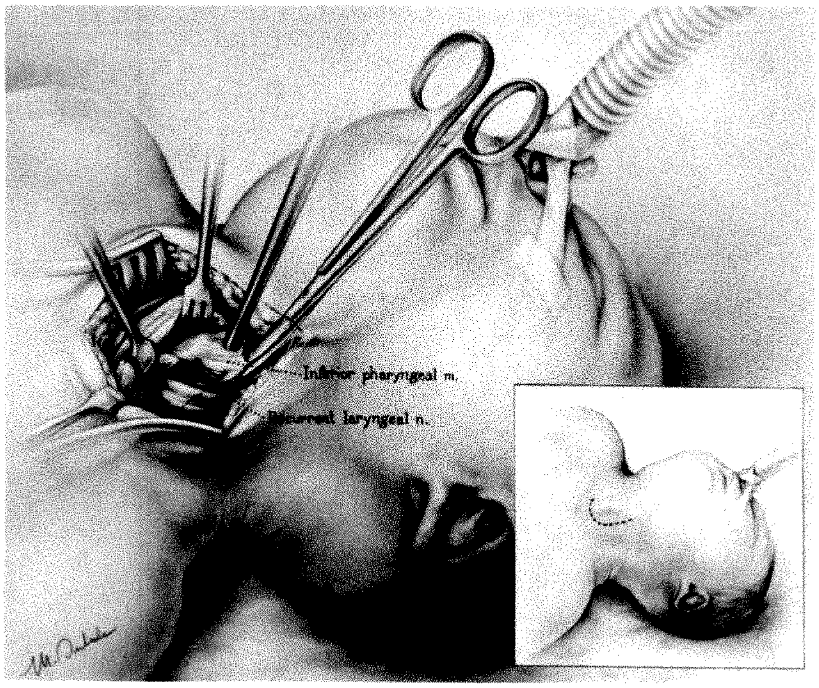

Fig 2. For repair a J-shaped incision was made along the sternomastoid muscle (inset). The inferior pharyngeal muscle was incised posteriorly to gain access to the cleft.

3A). The right and left ridges were approximated in the midline using interrupted 4-0 Vicryl sutures, completing septation to above the cricoid cartilage, making the epiglottic mechanism competent (Fig 3B). Then the cricoid cartilage was divided anteriorly and tissue was mobilized posterolaterally to widen the upper larynx (Fig 4).

Seven days later, laryngoscopy showed continued patency. A tracheostomy was not done at the primary repair; however, because of recurrent edema tracheostomy was required for extubation. The tracheostomy was eventually removed and the vocal cords appeared to function normally. Long-term endoscopic follow-up was not possible. Recurrent aspiration was curtailed adequately by the repair.

Comment

Esophageal atresia occurs with or without an associated tracheal fistula in 0.03% of live births. Although similar in embryogenesis, LTE clefts appear much more infrequently. Despite this, Cameron and Williams [1] found a 0.2% incidence of this condition in 2,000 pediatric autop-

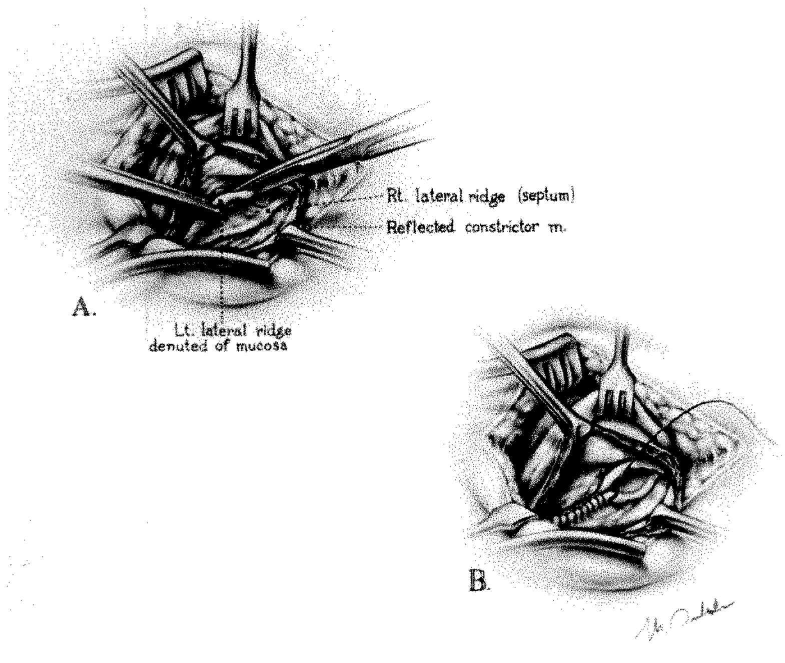
Rt. lateral ridge (septum)
Reflected constrictor m.
A.
Lt. lateral ridge denuded of mucosa
B.

Fig 3. (A) The right and left lateral ridges of the incomplete septum were denuded of mucosa and (B) sutured together with interrupted absorbable material.

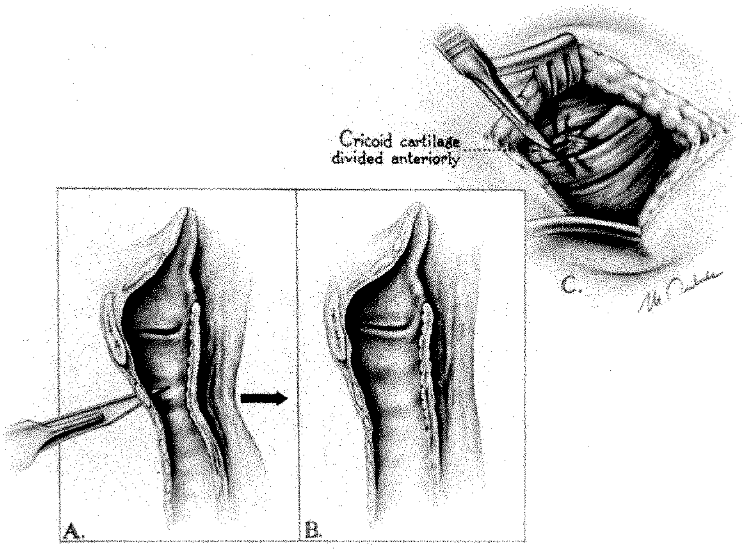

Fig 4. The cricoid cartilage was divided anteriorly (A), which allowed lateral displacement of soft tissues (C) effecting a wider tracheal passage (B).

sies. In 1792 Richter first described the LTE cleft, but by 1974 only 33 cases had been reported with 9 operative survivors [2, 3]. For the unsuspecting examiner the diagnosis has been difficult and may be missed using conventional radiographic studies. Delayed therapy often has resulted in early death. In infants having respiratory distress, continued difficulties with endotracheal tube position and ventilation may suggest either a large tracheoesophageal fistula or an LTE cleft.

By the embryonic third week the trachea, larynx, and upper esophagus become separated from the foregut anlage [2]. As pulmonary primordia separate from the foregut, a dorsal longitudinal groove forms and lateral ridges fuse in the midline, forming the tracheoesophageal septum. Separation into the trachea and esophagus proceeds cephalad, becoming complete by 33 days of development [2]. By the third month the cricoid cartilage fuses dorsally from fifth and sixth branchial arches. The hallmark of the LTE cleft relates to an arrest of both tracheoesophageal septation and dorsal cricoid fusion. Laryngotracheoesophageal defects may be limited to the larynx or extend to the carina. Recently, Kluth [4] detailed esophagotracheal separation abnormalities well, and categorized this one as a (X b1) fissure formation defect.

Bronchoscopy and esophagoscopy provide the best methods for an early diagnosis. In this patient flexible bronchoscopy was attempted; however, it was unhelpful because of an inability to ventilate and a lack of directivity. The esophageal Fogarty catheter helped define the distal limit of the incomplete tracheoesophageal septum.

Repair of this anomaly remains challenging and must be accomplished soon after diagnosis. In this patient refabrication of the upper tracheoesophageal septum was carried to above the cricoid. For septation, sufficient lateral tissue was available to prevent either esophageal or tracheal stenosis. To avoid narrowing the lower larynx, the anterior cricoid cartilage was split and lateral tissue was mobilized, widening the passage (Fig 4). Other authors [2, 3] have repaired upper LTE clefts by similar techniques; however, the division of the cricoid may represent a new approach. Recently, Donahoe and Gee [5] reported successful repair of a complete larynx to carina cleft. Correction of long LTE clefts has been rare as airway management remains difficult.

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Surgical Implications of Atrial Septal Defect Complicating Aortic Balloon Valvuloplasty

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An 80-year-old man underwent percutaneous transluminal balloon valvuloplasty for critical aortic stenosis. The procedure was performed by the antegrade atrial transseptal approach and was complicated by a persistent atrial septal defect. Symptoms recurred 6 months later, restenosis of the aortic valve was confirmed, and the atrial septal defect yielded a substantially greater left-to-right shunt. This complication of percutaneous transluminal balloon valvuloplasty poses important problems in hemodynamic assessment and operative management of patients who undergo subsequent aortic valve replacement.

(Ann Thorac Surg 1989;48:295–7)

Percutaneous transluminal balloon valvuloplasty (PTBV) is increasingly used for nonsurgical therapy of severe aortic stenosis in high-risk elderly patients. Although initial results appeared favorable, recent data raise serious questions regarding the long-term efficacy of this technique, primarily because of the high incidence of restenosis. In a recent report [1], 17 of 168 patients with initially successful PTBV for aortic stenosis required aortic valve replacement within 1 year. Increasing numbers of patients may therefore be referred to cardiothoracic surgeons for aortic valve replacement after PTBV failure.

Although aortic PTBV is usually performed by the retrograde aortic approach, an antegrade transvenous technique has also been used [2]. This requires puncture and dilation of the atrial septum with passage of balloon dilation catheters across the septum and manipulation through the aortic valve. In this report, we describe the creation of an atrial septal defect (ASD) during an antegrade aortic PTBV that demonstrated an increase in size concomitant with valvular restenosis 6 months after the procedure.

An 80-year-old man with previous anterior myocardial infarction and repair of an abdominal aortic aneurysm was seen with New York Heart Association functional class IV symptoms of congestive heart failure, exertional angina, and presyncope. Diagnostic cardiac catheterization revealed critical aortic stenosis with an aortic valve area of 0.7 cm^2 by the Gorlin formula [3]. Angiography revealed severe anterior wall akinesis, mild mitral and aortic valve insufficiency, and occlusion of the proximal left anterior descending coronary artery. In view of his age, depressed ventricular function, and overall status, the patient was considered to be at high risk for operation and was referred for PTBV.

At the time of aortic PTBV, inability to advance any guidewire retrogradely above the level of the aortoiliac bifurcation necessitated an antegrade atrial transseptal approach. A complete hemodynamic study before PTBV confirmed the diagnosis of severe aortic stenosis. With an 8F transseptal sheath and Brockenbrough needle, we performed an atrial septal puncture by standard technique from the right femoral vein. Atrial septal dilation was performed with a balloon dilation catheter 8 mm in diameter and 3 cm long (Mansfield Scientific). Four balloon dilations of the aortic valve were performed using a 9F balloon catheter 20 mm in diameter and 5.5 cm long (Mansfield Scientific), which was passed antegrade over a guidewire through the dilated atrial septum.

Table 1 summarizes the hemodynamic and oximetric analyses performed before and immediately after PTBV. The procedure resulted in a decrease in mean aortic valve gradient from 28 to 20 mm Hg and in peak aortic valve gradient from 35 to 21 mm Hg, with an increase in the thermodilution cardiac output from 4.1 to 7.4 L/min. However, serial oximetric sampling at the completion of the procedure revealed a significant oxygen step-up at the right atrial level, with a pulmonic–systemic flow ratio (Q_P/Q_S) of 1.8:1. Using the Fick systemic blood flow technique [4], the valve area after PTBV was 1.2 cm^2.

The patient experienced substantial functional improvement after PTBV and was in functional class II at 2-month follow-up. However, 6 months after the initial PTBV, he had two episodes of syncope. Repeat cardiac catheterization revealed extensive restenosis. In addition, a clinically significant residual left-to-right intracardiac shunt was demonstrated at the atrial level with a Q_P/Q_S of 2.8:1. Using the Fick systemic blood flow technique, the calculated aortic valve area was 0.8 cm^2. In view of his recurrent symptoms, restenosis of the aortic valve, and presence of a large traumatic ASD, the patient was referred for operation.

At operation, the superior and inferior vena cavae were cannulated individually for venous return to the pump oxygenator. After cross-clamping, the aorta was opened

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Table 1. Summary of Hemodynamic and Oximetric Analyses

Variable	Before PTBV	After PTBV	Follow-up (6 mo)
Pressure			
RA (mm Hg)	2	4	10
RV (mm Hg)	65/4	33/5	64/14
PA (mm Hg)	65/22	33/10	64/21
Mean PA (mm Hg)	43	17	30
PCW (mm Hg)	31	6	19
LV (mm Hg)	158/22	129/10	165/15
AAo (mm Hg)	123/55	108/50	130/83
CO_{TD} (L/min)	4.1	7.4	6.2
SBF_F (L/min)	3.8	4.1	3.9
PAVG (mm Hg)	35	21	35
MAVG (mm Hg)	28	20	27
Calculated AVA (cm^2)	0.7	1.2	0.8
O_2 saturation (%)			
SVC	. . .	56.7	54.3
IVC	. . .	68.6	76.6
RA	. . .	64.1	88.5
PA	61.6	74.8	84.2
Arterial	96.6	94.9	96.5
Estimated Q_P/Q_S		1.8	2.8

AAo = ascending aorta; AVA = aortic valve area; CO_{TD} = thermodilution cardiac output; IVC = inferior vena cava; LV = left ventricle; MAVG = mean aortic valve gradient; PA = pulmonary artery; PAVG = peak aortic valve gradient; PCW = pulmonary capillary wedge; PTBV = percutaneous transluminal balloon valvuloplasty; Q_P/Q_S = ratio of pulmonic to systemic flow; RA = right atrium; RV = right ventricle; SBF_F = systemic blood flow by Fick technique; SVC = superior vena cava.

and cardioplegic solution was delivered directly into the coronary ostia with hand-held cannulas. The right atrium was opened, and a 3-cm long tear of the atrial septum was found in the region of the fossa ovalis. This was repaired primarily with interrupted mattress sutures. The patient's aortic valve was tricuspid and tightly stenotic, with severe calcification and fusion of the leaflets. The valve was replaced with a 21-mm Carpentier-Edwards bioprosthesis, and the patient's postoperative course was uncomplicated.

Comment

Incidence of Atrial Septal Defect Complicating Percutaneous Transluminal Balloon Valvuloplasty

Iatrogenic ASD occurs as a component of mitral valve PTBV, consequent to the requirement of a transseptal atrial approach, and results in left-to-right shunts in up to one third of patients [5]. The hemodynamic effects of such shunts are frequently small, with Q_P/Q_S ratios of less than 2.3:1 [6], and these shunts are reported to disappear within several days after the procedure. Aortic PTBV is usually performed by the retrograde aortic approach. However, vascular trauma is a well-recognized complication of this technique, requiring surgical vascular repair in up to 15% of patients [1]. In an effort to decrease the incidence of this complication, some investigators have advocated use of the transseptal approach for PTBV [2].

The need for subsequent mitral valve replacement after PTBV of the mitral valve appears to be much less common than the need for subsequent aortic valve replacement after aortic PTBV [7]. In patients who undergo subsequent mitral valve replacement after PTBV, the presence of an ASD should be discovered during routine exploration of the left atrium. However, this is not the case with the post-PTBV patient who undergoes subsequent aortic valve replacement. Unless an effort is made to detect the presence of an ASD by preoperative studies, it may go undetected, thus affecting several hemodynamic and surgical considerations.

Hemodynamic Considerations

During follow-up hemodynamic assessment of a patient who has undergone aortic PTBV, the presence of an unrecognized residual ASD would lead to inaccurate assessment of aortic valve area and thus interfere with the diagnosis of restenosis. If only thermodilution cardiac outputs, or Fick cardiac outputs obtained by using pulmonary arterial oximetric samples, were used for estimation of systemic blood flow, an unrecognized ASD would result in substantial overestimation of transaortic blood flow and consequently overestimation of the aortic valve area (using the Gorlin formula) [3]. Thus, it is essential that serial oximetric samples be obtained from the inferior and superior vena cavae, right atrium, pulmonary artery, and systemic artery for detection of a left-to-right shunt at the atrial level [4]. If such an oxygen step-up is detected, the Flamm equation [8] for estimating best mixed venous oxygen saturation immediately proximal to the site of the shunt must be used to calculate the true arterial-mixed venous oxygen content difference, and subsequent calculation of systemic blood flow must be made by the Fick method. In our patient at 6-month follow-up (Table 1), the determination of cardiac output (6.2 L/min) by the thermodilution method was much greater than the true systemic blood flow (3.9 L/min) as determined by the Fick method. The most accurate determination of aortic valve area by the Fick method of systemic blood flow calculation yielded a valve area of 0.8 cm^2, whereas determination by the thermodilution method alone would have yielded a valve area of 1.2 cm^2. Thus, failure to recognize the presence of this defect could lead to overestimation of the patient's cardiac output and consequent underestimation of the severity of valve stenosis.

Surgical Considerations

Preoperative determination of the presence of an ASD in patients undergoing aortic valve replacement after PTBV is also important for surgical considerations. The presence of an ASD affects decisions regarding cardiopulmonary bypass techniques and methods for delivering cardioplegia.

Most surgeons use a single two-stage right atrial cannula for venous drainage during simple aortic valve replacement, which could be dangerous if an unsuspected ASD exists. After institution of cardiopulmonary bypass and opening of the aorta, aspiration of air from the left heart could result in an air-lock in the venous line and abrupt discontinuation of cardiopulmonary bypass. This potentially lethal hazard can be avoided by separate caval cannulation if the ASD is recognized preoperatively.

Retrograde cardioplegia infusion through the right atrium has been recommended for patients with aortic stenosis and concomitant aortic insufficiency [9]. However, when this route is attempted in patients with ASDs, shunting of cardioplegia into the left atrium occurs and ineffective myocardial protection results. If the ASD is not recognized preoperatively, rapid conversion to another administration technique (ie, by coronary ostial infusion or directly into the coronary sinus) would be required.

Finally, the presence of an ASD may complicate efforts to wean patients from cardiopulmonary bypass. The degree and direction of shunting through the unrepaired defect depends on relative compliances of the left and right cardiac chambers. With chronic ventricular pressure overload from aortic valve disease, left atrial and ventricular compliances would be decreased and could result in substantial left-to-right shunting and right heart volume overload with attendant difficulties in weaning from bypass.

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Successful Diagnosis and Surgical Treatment of Single Ventricle, Truncus Arteriosus

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The association of single ventricle and truncus arteriosus is rare. We present the successful surgical palliation of a patient who echocardiographically and angiographically has a truncus arteriosus type I and single left ventricle. At operation, the main pulmonary artery was dissected off the truncus arteriosus, and a 4-mm polytetrafluoroethylene graft was placed from the ascending aorta to the left pulmonary artery. The patient is currently 13 months old and growing well.

(Ann Thorac Surg 1989;48:298–300)

The association of single ventricle and truncus arteriosus is rare. Although isolated cases of this lesion have been reported, most of these cases are truncus arteriosus and single ventricle with only one atrioventricular valve [1–5]. In 1952, Siddoway and Chernish [6] reported 3 cases of single ventricle and truncus arteriosus. However, Van Praagh and Van Praagh [7] in 1965 reviewed all previously reported cases of single ventricle and truncus arteriosus, and found no convincing evidence that any of these cases with truncus arteriosus represented a single ventricle in which both atrioventricular valves or a common atrioventricular valve open into one ventricular chamber. This definition of single ventricle excludes cases of mitral or tricuspid atresia. All reported patients have been autopsy cases, and we are aware of no reported survivors of this lesion. We present the case of a child born with truncus arteriosus with a double-inlet single ventricle of the left ventricular type who underwent surgical palliation and is currently doing well.

This 3,720-g infant was born at 38 weeks of gestation and had a heart murmur and respiratory distress on the first day of life. Physical examination showed a tachypneic, acyanotic infant with full pulses. There was an increased right ventricular impulse. The systolic first sound was normal; the systolic second sound was single. There was a short grade 2/6 systolic ejection murmur present at the upper left sternal border, and a third heart sound was present at the apex. A prominent systolic ejection click was noted at the upper left sternal border. A chest roentgenogram showed mild cardiomegaly and normal pulmonary vascular markings. The electrocardiogram demonstrated a superior axis with counterclockwise loop and left ventricular hypertrophy. An echocardiogram demonstrated two atria with two atrioventricular valves and a moderately large secundum atrial septal defect (Figs 1, 2). The atrioventricular valves emptied into a large single ventricle of the left ventricular type. There was a single persistent truncus arteriosus, type I, arising from the ventricle and giving rise to the pulmonary arteries. There were also right and left superior vena cavae draining into right and left atria, respectively. Cardiac catheterization performed on the second day of life demonstrated a double-inlet left ventricle with an infundibular chamber from which arose the truncus arteriosus, type I (Fig 3). The atrial appendages appeared to be juxtaposed. After catheterization, the patient was discharged in good condition. She returned at 3 months of age with a respiratory syncytial virus pneumonia and congestive heart failure. She was treated with anticongestive and ribavirin therapy. After ten days of treatment, she recovered from her pneumonia and 1 week later underwent cardiac operation.

At operation, the main pulmonary artery was found to be rather short and wide, and originated from the posterolateral aspect of the truncal root (Fig 4). The atrial

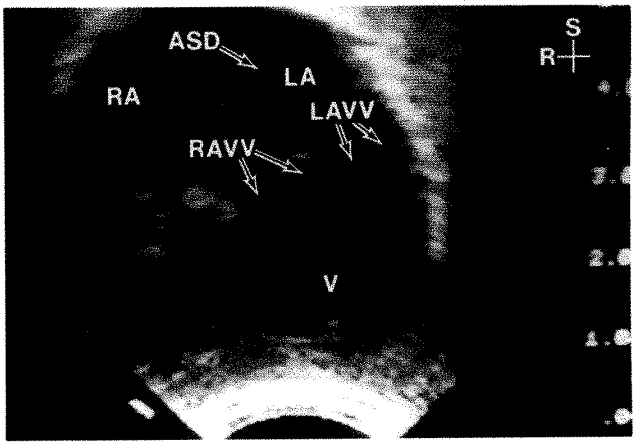

Fig 1. Apical four-chamber two-dimensional echocardiogram shows single ventricle with two atrioventricular valves. (ASD = secundum atrial septal defect; LA = left atrium; LAVV = left atrioventricular valve; R = right; RA = right atrium; RAVV = right atrioventricular valve; S = superior; V = single ventricle.)

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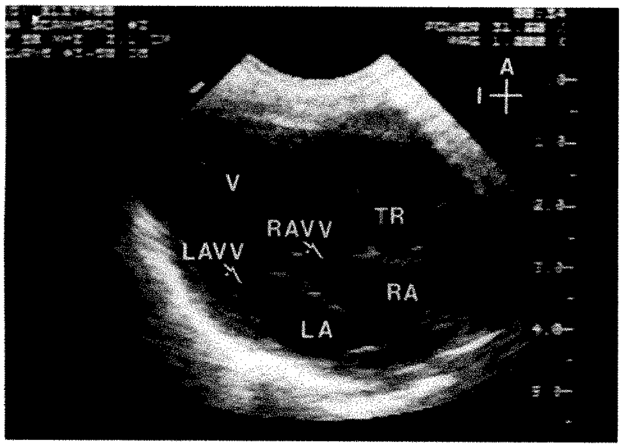

Fig 2. Long-axis two-dimensional echocardiogram shows two atrioventricular valves emptying into a single ventricle, which gives rise to the truncus arteriosus. (A = anterior; I = inferior; LA = left atrium; LAVV = left atrioventricular valve; RA = right atrium; RAVV = right atrioventricular valve; TR = truncal root; V = single ventricle.)

appendages were juxtaposed. Cardiopulmonary bypass was instituted, and the main pulmonary artery was dissected off the truncus arteriosus. The aorta was then closed with a running suture, and the main pulmonary artery was closed with a piece of pericardium that had been fixed in glutaraldehyde. A 4-mm polytetrafluoroethylene graft was then placed from the ascending aorta to the left pulmonary artery (Fig 4). The patient was weaned from cardiopulmonary bypass without incident and transported to the intensive care unit in good condition. The patient was extubated four days later and discharged from the hospital 17 days after her operation in good condition.

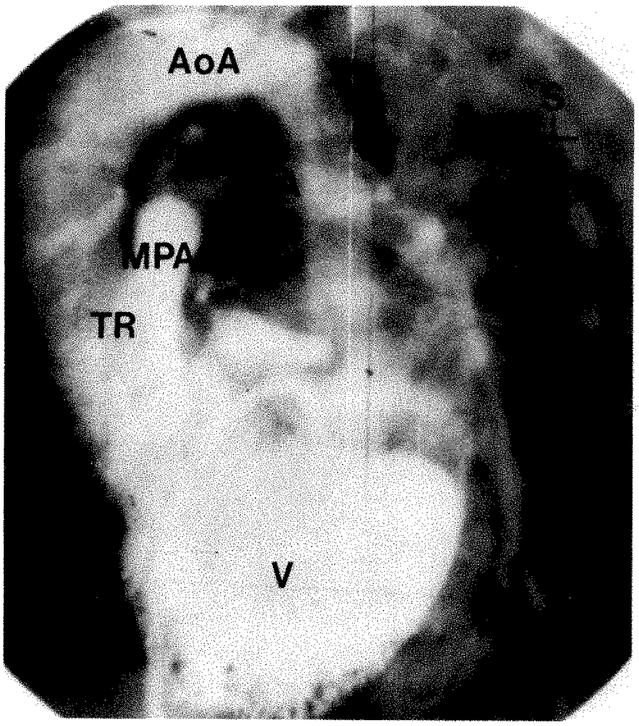

Fig 3. Lateral angiogram of contrast injection into the single ventricle shows the truncal root arising from the single ventricle and giving rise to the pulmonary arteries and aortic arch. (AoA = aortic arch; LPA = left pulmonary artery; MPA = main pulmonary artery; R = right; S = superior; TR = truncal root; V = single ventricle.)

Her medications at that time included digoxin, furosemide, and spironolactone. Since then, the patient has continued to do well and is presently 13 months old and growing well.

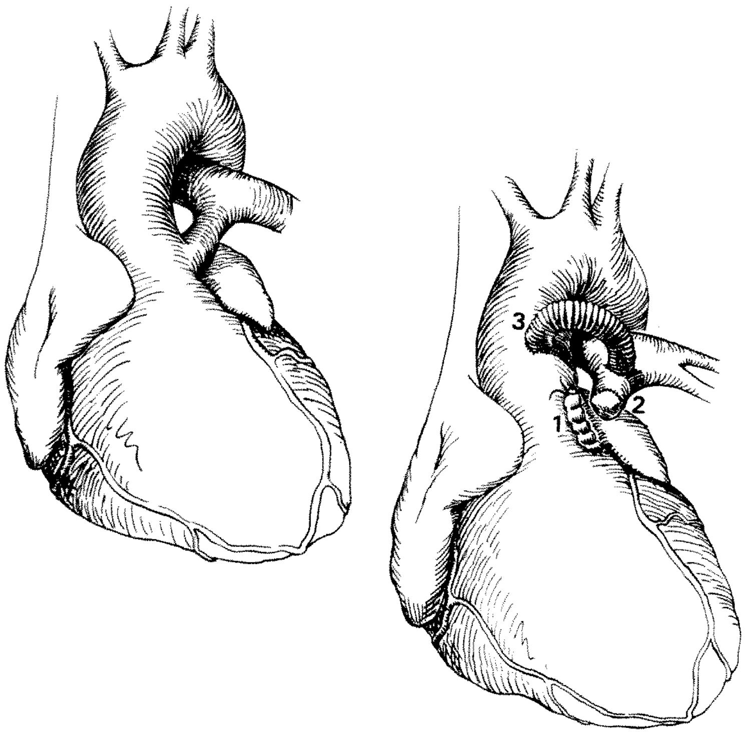

Fig 4. Anatomy before (left) and after (right) surgical palliation, which consisted of (1) removal of the main pulmonary artery from the truncal root and closure of the truncal root, (2) patch closure of the main pulmonary artery root, and (3) placement of a 4-mm polytetrafluoroethylene aortopulmonary shunt.

Comment

The combination of single ventricle and truncus arteriosus is rare. We describe the successful surgical palliation of a patient who echocardiographically and angiographically has a truncus arteriosus type I and single ventricle, with two atrioventricular valves emptying into a single ventricle of left ventricular morphology. We are not aware of any previous reports of successful surgical treatment of this lesion. Our planned treatment of this patient consists of a two-staged surgical approach. The first stage of the operation, as described, was performed to regulate pulmonary blood flow to protect the pulmonary vasculature from excess blood flow and pressures. In this manner, we hope to maintain adequate systemic oxygenation while not damaging the pulmonary vasculature for the second stage of the surgical treatment. Later, the patient will undergo cardiac catheterization so that we can estimate pulmonary artery flows, pressures, and resistances. If these are favorable, the patient will undergo the second stage of the repair, which will consist of closure of the aortopulmonary shunt, patch closure of the atrial septal defect and right atrioventricular valve, and connection of the right atrium to the pulmonary arteries. This will then give the patient separation of the circulations and physiological repair. At present, we believe that the patient's anatomy and physiology are favorable for this operation.

In summary, we present a patient with single left ventricle and truncus arteriosus who has been initially palliated by separation of the pulmonary artery from the truncal root and placement of an aortopulmonary shunt. Physiological repair will be accomplished by a Fontan-type procedure if hemodynamics are favorable.

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A Technique of Airway Management in Children With Obstructed Airway due to Tumor

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Airway management of patients with tracheobronchial compression due to mediastinal masses poses a difficult problem. A new technique of direct vision endotracheal intubation is described, and other adjunctive measures are reviewed.

(Ann Thorac Surg 1989;48:301–2)

Perioperative management of a partially obstructed airway in infants and children with mediastinal masses is a difficult and sometimes fatal problem. Death during and after anesthetic induction is well documented, often despite careful preoperative planning. We report a case of severe tracheobronchial compression due to a large mediastinal mass, successfully managed by a technique utilizing the Storz rigid bronchoscope as a stylet for a reinforced endotracheal tube. This technique is described, and principles of airway management if patients with mediastinal masses are reviewed.

Case Presentation

The patient is a 15-year-old girl with a history of Hodgkin's lymphoma in remission for several years. At follow-up, she had a large mass in the anterior and middle mediastinum, with tracheal compression and deviation of the trachea to the right. An exploratory thoracotomy was planned for diagnostic purposes.

Endotracheal intubation was accomplished with a 6 mm × 35-cm Storz rigid bronchoscope as the stylet for a reinforced 7-mm endotracheal tube. With this technique, the reinforced endotracheal tube was fitted over the rigid ventilating bronchoscope. The entire unit was then advanced through the vocal cords under direct visualization. An area of severe compression just below the vocal cords was noted. The bronchoscope was gently advanced beyond this compression into a widely patent trachea. The endotracheal tube was left in place, and the bronchoscope was withdrawn. The exploratory thoracotomy was performed, and the patient recovered uneventfully.

Comment

Mediastinal masses may cause serious tracheobronchial compression. Children with symptoms of upper respiratory obstruction from a mediastinal mass have tracheal narrowing and a decrease in tracheal cross-sectional area of 35% or greater [1]. This is associated with sudden death due to loss of the airway during induction of or emergence from general anesthesia [1].

In 1973, Amaha and colleagues [2] presented the earliest published report of major tracheobronchial obstruction by a mediastinal tumor. Since then, other cases have been described, including lymphosarcomas, Hodgkin's disease, and neuroblastomas. All these reports emphasize the difficulty in managing such patients perioperatively. Even meticulous preoperative planning has not guaranteed success. Several important guidelines have emerged, however, that may decrease perioperative complications and mortality.

Mechanical management of the airway itself may represent the most acute problem. Simple endotracheal intubation under direct laryngoscopy may be possible, but may not be helpful in cases of distal tracheobronchial compression or angulation. The technique we describe of rigid bronchoscopic intubation with a surrounding endotracheal tube can be life-saving. With this technique, an appropriately sized reinforced endotracheal tube is first fitted over the rigid ventilating bronchoscope. The entire unit is then advanced into the oropharynx under direct laryngoscopy. Once the bronchoscope has passed the vocal cords, the tracheobronchial tree is examined carefully for degree and length of compression or angulation. The bronchoscope is then advanced beyond the most distal point of obstruction, the endotracheal tube is left in place, and the bronchoscope is withdrawn. The technique is shown in Figure 1. Alternately, rigid bronchoscopy may be performed alone, as a guide to subsequent intubation, in infants and smaller children whose airways are too small to accept a rigid bronchoscope within the available sizes of reinforced endotracheal tubes.

We wish to emphasize, however, that routine diagnostic bronchoscopy is extremely hazardous in these airway-compromised patients [3]. Diagnostic bronchoscopy therefore should not be performed routinely in children with mediastinal masses, and the technique we describe is not a panacea for this difficult and potentially life-threatening problem. The technique, however, may aid airway control and general anesthesia in children who are judged to be good candidates for surgical resection.

Several reports describe other unique means of handling particularly difficult distal lesions. Amaha and colleagues [2] describe use of one-lung ventilation in a patient with severe one-sided obstruction. They also report, however, that in cases of lesser obstruction, one-

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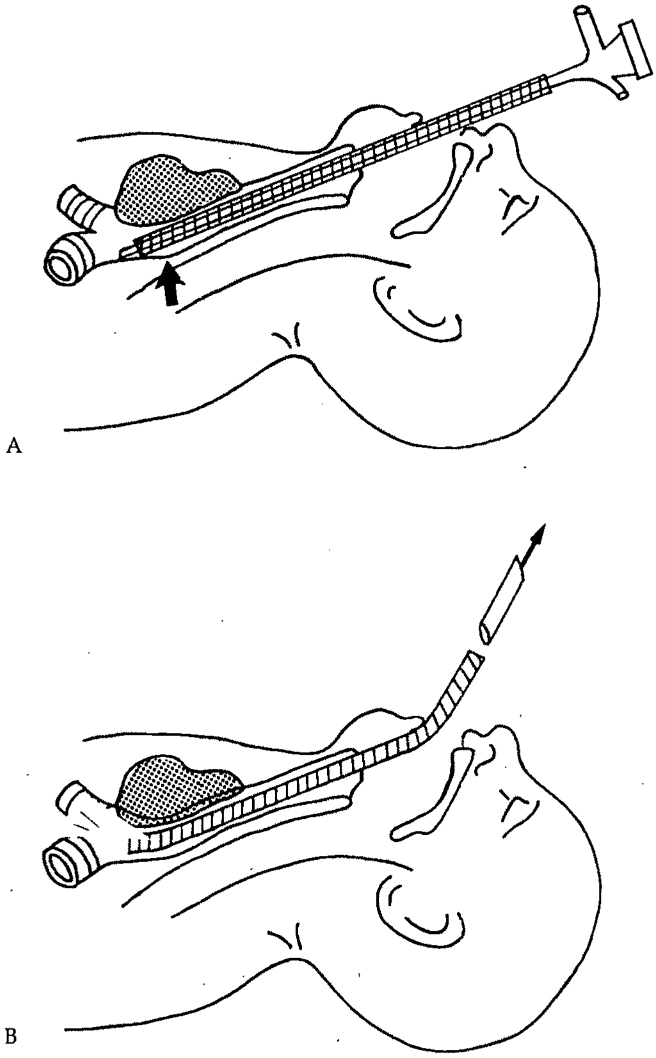

Fig 1. Technique of bronchoscopic intubation. (A) A reinforced endotracheal tube is fitted over the ventilating bronchoscope. The entire unit is advanced through the vocal cords under direct visualization and beyond the area of tracheal compression/deviation (arrow) *into patent trachea. (B) The endotracheal tube is left in place, and the bronchoscope is withdrawn.*

lung ventilation usually results in marked hypoxia due to subsequent right-to-left shunting in the underventilated lung. Todres and co-workers [4] reported an ingenious scheme of coupled endotracheal and endobronchial ventilation through the oropharynx and a tracheostomy. Other investigators have described use of oxygen-jet ventilation, temporary partial cardiopulmonary bypass, and femorofemoral cardiopulmonary bypass during operative management of critical airway obstruction.

The effects of anesthesia and paralyzing agents on diaphragmatic mechanics and pulmonary ventilation contribute substantially to the risks in managing airway-obstructed patients. Diaphragmatic and intercostal muscle paralysis markedly decreases the lung functional residual capacity by causing a cephalad diaphragmatic displacement, particularly in the supine position. General anesthetic agents have also been shown to relax tracheal smooth muscle [5]. On induction of anesthesia, the physiological effect of these changes is intensified in the airway-compromised patient. Therefore, avoidance of muscle relaxants, use of the semi-Fowler or lateral decubitus positions, and maintenance of spontaneous respiration may be important perioperative measures [6].

Finally, preoperatively decreasing the tumor burden or associated inflammation by noninvasive means, such as corticosteroids, radiation therapy, or chemotherapy may be helpful, depending on the specific type of tumor involved [1]. These methods can diminish the amount of tracheal deviation and widen the tracheobronchial lumen, allowing greater ease of intubation and subsequent airway management.

In summary, large or unusually located mediastinal masses may present serious and sometimes fatal problems regarding perioperative airway management. Successful guidelines in managing airway-obstructed patients include the following. (1) General anesthesia should be avoided through use of local anesthesia for biopsy and noninvasive diagnostic studies whenever possible. (2) A preoperative course of intravenous steroids, radiation therapy, or chemotherapy can be used, when applicable, to diminish tracheobronchial compression, deviation, or both, and to lessen the effects of general anesthesia on respiratory dynamics. (3) Muscle relaxants should be avoided. (4) Maintenance of spontaneous respiration should be continued until the airway is secure and the ability to deliver manual ventilation is assured. (5) The semi-Fowler's or lateral decubitus position should be used during induction of anesthesia. (6) A reinforced endotracheal tube should be used when possible. (7) Routine diagnostic bronchoscopy, which is hazardous in children with mediastinal masses, should not be performed. (8) Bronchoscopic intubation as a stylet for a reinforced endotracheal tube can be helpful in passing the tube beyond a distal point of obstruction. (9) Rigid bronchoscopy alone, as a guide to subsequent immediate endotracheal intubation, may also be used in selected cases of distal airway obstruction, particularly in infants and small children whose airways are too small to accept the endotracheal tube-over-bronchoscope complex. This allows assessment of the length and degree of tracheal obstruction.

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An Anterior Longitudinal Aortotomy With a Distal Aortic Transection for the Arterial Switch Operation

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An additional longitudinal aortotomy on the anterior aspect of the old ascending aorta after distal aortic transection is very effective for removal of the coronary buttons, prevention of deformation of the neopulmonary arterial ring, and reconstruction of the neopulmonary arterial trunk after the Lecompte maneuver, especially for the neonatal arterial switch operation.

(Ann Thorac Surg 1989;48:303–4)

There are several methods of aortic transection of the ascending aorta and removal of coronary buttons in the arterial switch operation [1–3]. After transecting the aorta more than 10 mm superior to the valval commissure, we place an additional aortotomy that runs longitudinally on the ventral aspect of the ascending aorta. This incision facilitates removal of the coronary buttons in a good operative field and makes reconstruction of the neopulmonary artery easier after the Lecompte maneuver [4], especially in the neonatal arterial switch operation. Three consecutive neonates (the first patient had simple transposition of the great arteries with a single coronary artery [Shaher 3a], the second had transposition of the great arteries with a ventricular septal defect, and the third had simple transposition of the great arteries with a single coronary artery [Shaher 3c]) were recently operated on with this technique with good results.

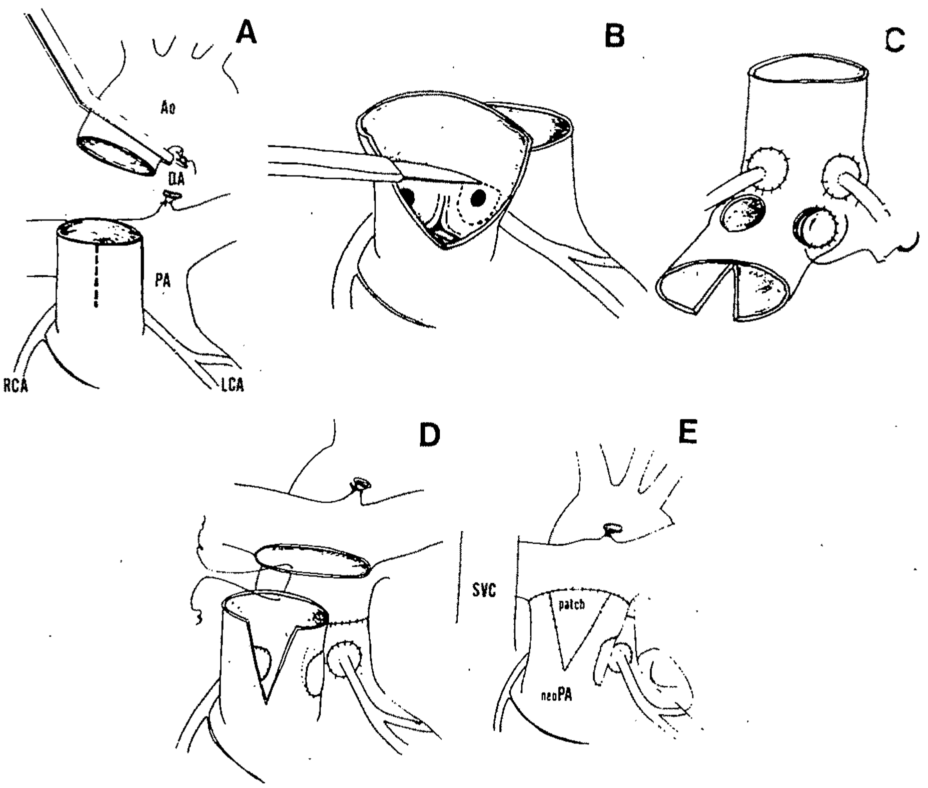

Fig 1. (A) After the ascending aorta is transected, an additional longitudinal aortotomy on the anterior aspect is added toward the nonfacing sinus of Valsalva (broken line)*. This aortotomy is not extended to the level of the commissure of the aortic valve. (B) The coronary buttons are removed in a good operative field through the aortotomy. (C) The defects left by removal of the coronary buttons are filled in separately. (D) The posterior walls of the neopulmonary artery are anastomosed directly. (E) In our 3 patients, we were able to enlarge the neopulmonary artery easily with a triangular patch placed on the anterior aspect.* (Ao *= aorta;* DA *= ductus arteriosus;* LCA *= left coronary artery;* PA *= pulmonary artery;* RCA *= right coronary artery;* SVC *= superior vena cava.)*

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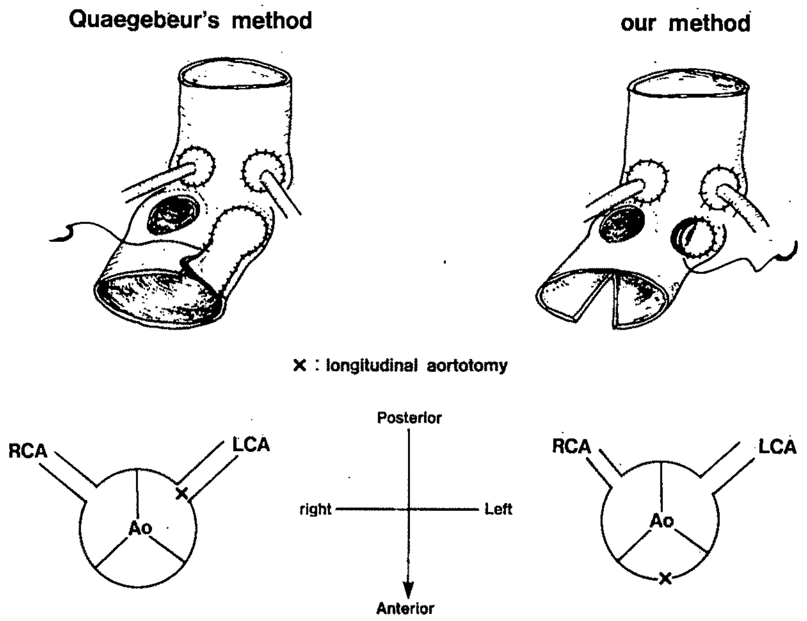

Fig 2. By the method of Quaegebeur and associates [2] a longitudinal aortotomy is added on the lateral or posterior aspect and the defects of the buttonholes are closed with dorsally placed patches, one tongue-shaped and the other circular. On the other hand, with the new method using an anterior longitudinal aortotomy, the defects of the buttonholes are closed with two circular patches. (Ao = *aorta;* LCA = *left coronary artery;* RCA = *right coronary artery.)*

Technique

After establishment of cardiopulmonary bypass, the ductus arteriosus is divided. The ascending aorta is clamped and divided as far distally as possible. We add an additional longitudinal aortotomy on the anterior aspect from the aortic transection site to a level just superior to the nonfacing sinus of Valsalva (Fig 1A). Good visualization of the coronary ostia and valve leaflets is obtained, and coronary buttons are removed without difficulty (Fig 1B). The coronary buttons are implanted onto the neoaorta, and the aortic cross-clamp is released after the neoaorta is reconstructed by the Lecompte maneuver. The defects of the buttonholes on the dorsal aspect of the neopulmonary artery are filled with circular patches of porcine pericardium (Polystan A/s, Ballerup, Denmark) (Fig 1C). The neopulmonary arterial trunk is reconstructed, with direct anastomosis of two segments of the neopulmonary artery if possible. Enlargement of the neopulmonary artery, if necessary, is finally accomplished by placing a patch on the anterior aspect without difficulty (Fig 1D, E).

Comment

We transect the ascending aorta as far distally as possible in accordance with the method of Quaegebeur and associates [2], because we like to anastomose the proximal old aortic segment directly to the distal old pulmonary segment to allow growth. This method also has the advantage of avoiding deformation of the neopulmonary artery and coronary arteries by compression of the posteriorly located neoaorta after the Lecompte maneuver. The greater the length between the transected level of the aorta and coronary ostia, however, the more difficult the removal of the coronary buttons. Quaegebeur's aortotomy is performed from the transection site down toward the most anterior coronary ostium. By the method of Quaegebeur and associates, in patients with an anteroposterior relationship of the great arteries, the defects of the buttonholes are closed with dorsally placed patches, one tongue-shaped and the other circular (Fig 2). At times it is difficult to design the tongue-shaped patch suitably for the final form of the neopulmonary artery, and deformation of the neopulmonary arterial ring and postoperative bleeding at the region of the tongue-shaped patch may result. On the other hand, our additional longitudinal aortotomy on the anterior aspect of the ascending aorta in combination with distal aortic transection has the following advantages: (1) With our method, the resultant degree of deformation at the neopulmonary arterial ring is less than that of other methods because this aortotomy does not cross the line of the old aortic valval commissure; and (2) this method allows anastomosis of the posterior wall of the neopulmonary artery directly and easy addition of a separate anterior patch if needed so that possible bleeding from the suture line of the patch is easily controlled.

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Reoperative Median Sternotomy

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Sternal reentry for reoperative cardiac procedures poses a substantial risk of technical problems. A simple technique for sternal reentry is described that is both expeditious and safe.

(Ann Thorac Surg 1989;48:305)

Reoperation for cardiac procedures usually necessitates reentering the chest through a median sternotomy. Operative mortality is generally increased for redo procedures. As evident from data from the Coronary Artery Surgery Study [1], the increased mortality associated with reoperative coronary procedures is primarily due to a greater risk of death on the day of operation. Operative mortality on the day of a redo coronary bypass was 3.9% compared with 1.1% on the day of the initial procedure. After the day of operation, surgical mortality was approximately the same for a reoperative (1.4% mortality) or an initial (2.0% mortality) procedure.

Although many factors contribute to this increased risk on the day of reoperation, accidents at the time of sternal reentry may play a major role [2]. Not uncommonly, the right ventricle, aorta, or patent grafts may be adherent to the posterior table of the sternum and vulnerable to injury at the time of reentry.

We have used a simple technique that essentially avoids many potential accidents at the time of sternal reentry (Fig 1). The previously placed sternal wires are cut or untwisted but not removed. An oscillating saw is then used to divide the sternum while upward traction is applied to the untwisted wires. Not only does the upward traction help elevate the sternum away from the mediastinal contents, but the wires themselves serve as a barrier to the saw at the posterior table of the sternum. When the saw encounters the wires posteriorly, a characteristic vibration in the wire and grating noise is immediately obvious to the surgeon. When the bone has been divided throughout its length, the wires may then be removed and mediastinal dissection started in the usual fashion.

We have used this technique in our last 50 consecutive patients without incident. Sternal reentry may be accomplished in this manner more expeditiously and with increased safety.

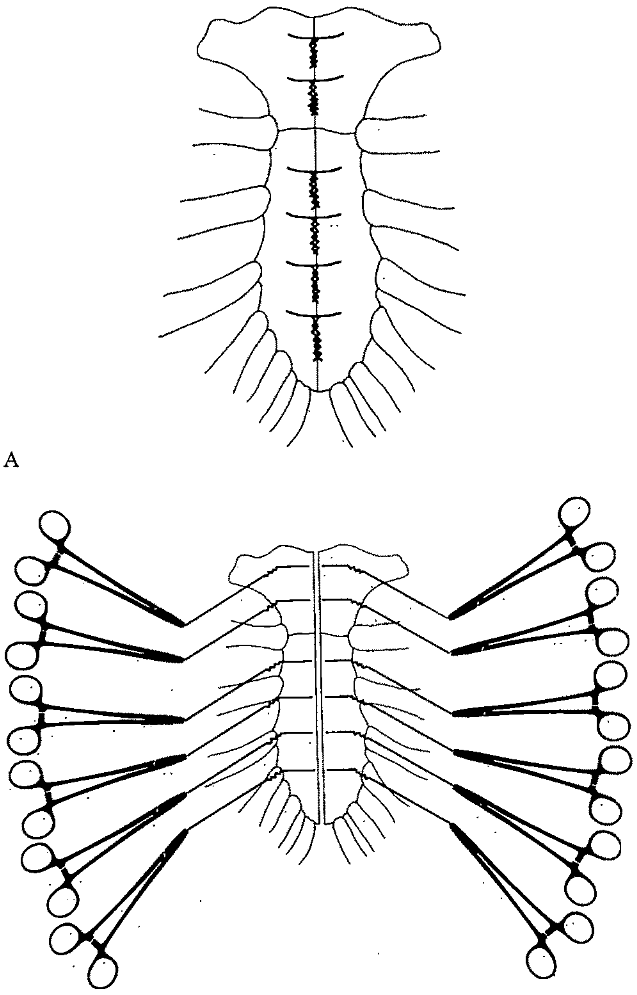

Fig 1. (A) The previous sternal wires are exposed through a midline incision. (B) The wires are untwisted or cut but not removed. An oscillating saw may then be used to divide the sternum. The wires provide a barrier to the saw and are removed after the sternum is divided.

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Empyema Thoracis: Historical Perspective

Richard M. Peters, MD

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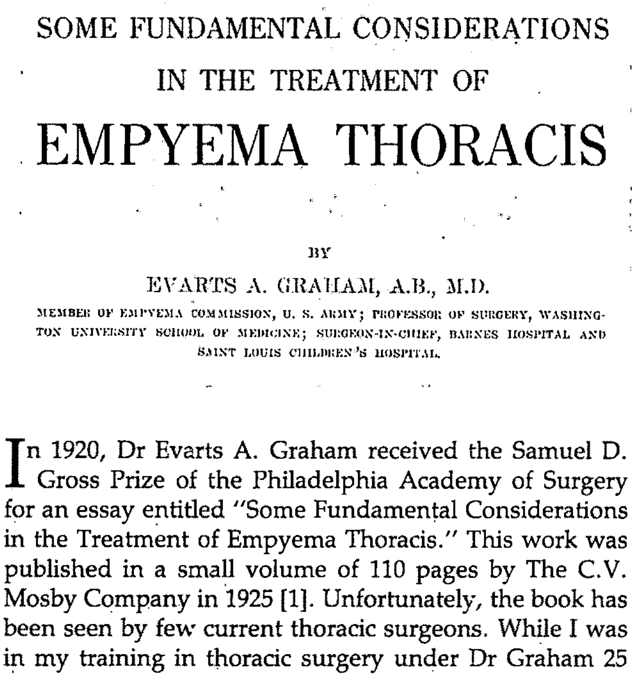
The historical monograph described in this article presents a brilliant piece of work by a young surgeon. To stop the carnage of opening drainage for acute streptococcal empyema, Dr Evarts A. Graham identified the relation between lung mechanics and open chest drainage and the reasons for the stiff lung. This gem of a book shows how thoughtful experimental study with simple tools can produce answers to important clinical problems.

(Ann Thorac Surg 1989;48:306–8)



SOME FUNDAMENTAL CONSIDERATIONS
IN THE TREATMENT OF
EMPYEMA THORACIS

BY
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In 1920, Dr Evarts A. Graham received the Samuel D. Gross Prize of the Philadelphia Academy of Surgery for an essay entitled "Some Fundamental Considerations in the Treatment of Empyema Thoracis." This work was published in a small volume of 110 pages by The C.V. Mosby Company in 1925 [1]. Unfortunately, the book has been seen by few current thoracic surgeons. While I was in my training in thoracic surgery under Dr Graham 25 years after the publication of this book, my mother, a medical historical librarian, found a copy for me which Dr Graham autographed. It is a remarkable historical document of a man's use of careful study to change military medicine and reduce preventable mortality. It has seven sections: Introduction, 2 pages; Pathology, 52 pages; Prevention of chronic empyema, 14 pages; Careful attention to the nutrition of the patient, 5 pages; Discussion, summary, and conclusions, 3 pages; and Addendum, 22 pages. The principles set down in this monograph provided an extraordinary advance in surgical therapy.

During the winter of 1917 to 1918, "an epidemic of hemolytic streptococcus infections of the respiratory tract . . . . ravaged the military camps of this country."* This epidemic "did much to clarify the general understanding of not only the pathology but also the treatment of empyema." The US Army set up an empyema commission to study this problem. Fortunately, Dr Evarts A. Graham as a young surgeon was appointed to this commission. He capitalized on "this opportunity of studying intensively and under proper control a large number of cases," and developed "certain principles" that came "into general recognition" which, although most of them "were not new, . . . resulted in more or less standard methods of treatment." "Following their application in the Army, the mortality rate dropped from an appallingly high figure to one remarkably low."

In 1906, the reported mortality of empyema in civilian life was in the range of 20%, and in February 1918, an Army survey showed it to be 30.2% overall, but ranging as high as 70% or more in camps in which early open drainage was standard. When the principles Dr Graham elucidated were applied by the empyema commission, the mortality was reduced to 3.4%.

> The essential points of these new principles are: (1) Careful avoidance of open pneumothorax in the acute stage, (2) The prevention of a chronic empyema by the rapid sterilization and obliteration of the infected cavity, and (3) Careful attention to the nutrition of the patient.

The 52 pages devoted to the pathology of empyema contain an extraordinary exposition of the basic principles governing the relation between lung mechanics, pleural dynamics, and ventilatory work. Modern pathophysiology has changed terminology and filled in some details, but the fundamentals are presented by Dr Graham.

He begins by pointing out the marked differences between pneumococcal and streptococcal empyema. He noted: "Pneumococcus empyema is almost always a complication of lobar pneumonia and it usually is not recognized until after the acute stage of the pneumonia has passed and at a time when probably the disappearance of much of the exudate from within the lung has increased the vital capacity over what it was during the active acute stage of the infection." Dr Graham defined vital capacity for his readers as "the maximal amount of air that can be exhaled after a maximal inhalation." He points out the difference between streptococcal pneumonia and pneumococcal pneumonia. Streptococci infect the bronchioles, resulting in patchy atelectasis. The obstruction of airways with streptococcal pneumonia is greater than in pneumococcal pneumonia. He reasoned that resultant stiff lungs would make open pneumothorax result in much greater harm. He therefore made some studies of open pneumothorax, starting with a study of normal intrapleural pressures. He gathered data that 70 years ago were not generally known: (1) that pleural pressure was subatmospheric throughout the ventilatory cycle, and (2) that the

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*All quotes in this article are from reference [1].

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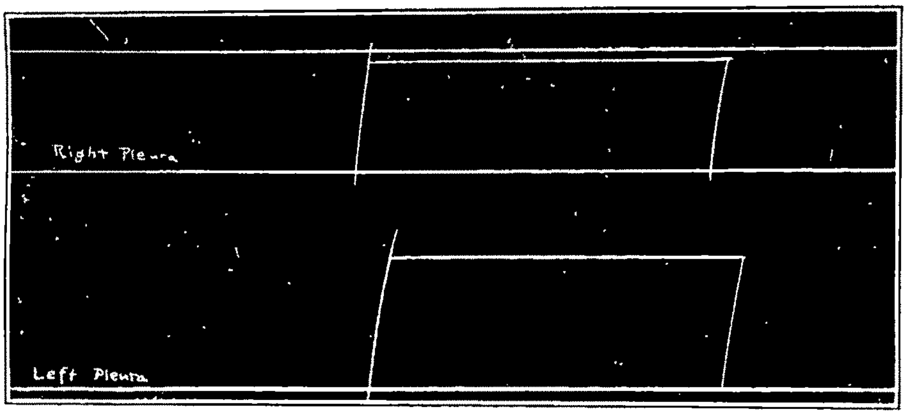

Fig 1. Tracing showing that when the left pleural cavity of a fresh adult human cadaver is inflated with air at a pressure of 10 cm H_2O, the right pleural cavity registers a pressure of 9 cm H_2O. The top line is a record of a pressure of 10 cm H_2O made with the tambour attached to the right pleural cavity. Calibration showed that the actual pressure was 9 cm H_2O. Reprinted from [1] by permission of The C.V. Mosby Co.

mediastinum was not a rigid divider between pleural cavities but that a near equilibrium of pressure existed between the pleural cavities with open pneumothorax (Fig 1).

He compared studies of human cadavers with those of canine cadavers, found these comparable, and proceeded with studies of open pneumothorax in dogs (Fig 2). He inserted a cannula attached to a tambour into the pleural cavity; the tambour was in turn attached to a kymograph and recorded pressure changes on smoked drums. He created wounds of different sizes in the chest cage of dogs to create open pneumothoraces, and measured both pleural pressures and airway pressures. He observed:

> The ability of the animal, therefore, to withstand an open pneumothorax is dependent upon his ability to compensate by increasing his respiratory effort. Obviously a strong, vigorous animal can compensate better than a weaker one. In our experience young adult dogs have uniformly withstood the harmful effects of an open pneumothorax better than old or weak and emaciated dogs.
>
> It is a very striking fact that usually the restoration of negative intrapleural pressure can be instantly accomplished, even in cases in which because of the size of the opening there is no negative pressure, merely by closing the pleural opening, thus making a closed instead of an open pneumothorax, provided that the duration of absence of negative pressure has not been so great that because of asphyxia the animal is too nearly dead to compensate for the relatively slight disturbance resulting from the closed pneumothorax. But here, again, the intrapleural pressure does *not* become so low as it was before the opening was made, at least not within a few minutes. Presumably it would become normal as soon as the air contained in the pleural cavity was absorbed; but this point has not been tested.

Dr Graham's summary and conclusions provide a succinct and lucid statement about empyema.

> Empyema in previous years has been one of the most serious problems in surgery, as judged by the mortality figures alone. The opportunities for the study of a large number of cases under favorable conditions in the military hospitals have resulted in modifications of treatment which give promise of not only greatly reducing the mortality but also the disability from this condition.
>
> The essential points of these new principles of treatment are: (1) Careful avoidance of open pneumothorax in the acute, pneumonic stage, (2) the prevention of a chronic empyema by the rapid sterilization and obliteration of the infected cavity, and (3) careful attention to the nutrition of the patient.
>
> Experimental work on pneumothorax, discussed in detail above, shows that previous conceptions of the mechanics of pneumothorax are erroneous. These conceptions have been based on the false idea that the mediastinum constitutes a more or less rigid partition between the two pleural cavities in the normal individual, and they have led to the belief that when an open pneumothorax is established the lung on the same side is collapsed and respiration is maintained by the other lung.
>
> On the contrary it has been shown by experiment on the human body that the mediastinum offers only a slight resistance when the pressure in one pleural cavity is made equal to that of a column of water 10 cm. high. Experiments with greater pressures than this have not been carried out.
>
> In the normal individual there is at all times practically an equilibrium of pressure throughout the whole thorax, so that when an open pneumothorax on one side is created both

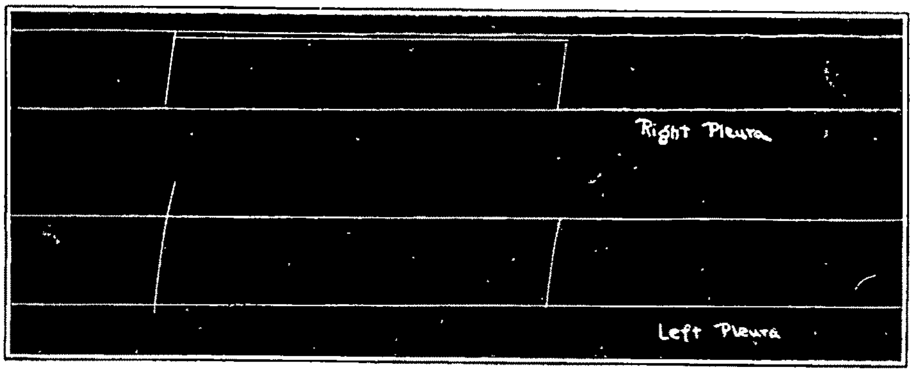

Fig 2. Tracing made in the same way with a recently killed dog, which shows that the dog is strictly comparable with the human, since here also the difference in pressure between the two pleural cavities amounted to only 1 cm H_2O. Reprinted from [1] by permission of The C.V. Mosby Co.

lungs are compressed and respiration is probably maintained by both lungs.

Obviously factors which tend to immobilize the mediastinum, such as adhesions and thickening from long-standing inflammation change these relationships by making of it a more rigid partition.

The maximum opening into a pleural cavity compatible with life depends upon a definite relationship which exists between the amount of air entering the lungs and the amount which enters the pleural opening. This may be approximately determined for the normal chest by the mathematical expression given in the text. By this expression it is found that an *average* normal human adult should be capable of withstanding for a short time an opening of about 511.5 sq. cm. (5 × 10 cm., or 2 × 4.11 inches), but in exceptional instances this value may be very much larger, depending to a considerable extent on the vital capacity. As in one instance, mentioned in the text, it may reach the very high value of 101.3 sq. cm. (15.6 sq. inches). The length of time that life will be maintained in the normal individual with a maximum opening will be determined largely by the strength of his respiratory muscles.

The bearing of these results and deductions upon both the treatment of acute empyema and upon thoracic surgery in general is obvious. Whenever the amount of air taken into the lungs is limited by the presence of an active pneumonia, with plugging of both air channels and alveoli, whenever there is an excessive demand for air, whenever there is sufficient weakening of the respiratory muscles to impair compensation or, in short, whenever the vital capacity is reduced, the size of a pleural opening compatible with life becomes smaller; and if any or all of the above factors are present in sufficient intensity, even a very small opening into the pleural cavity will produce death from asphyxia. Since all of these factors are likely to be present to a high degree during the early stage of an empyema of the streptococcus type, early operation with the establishment of an open pneumothorax carries with it an unwarrantable danger.

Other important effects of an open pneumothorax are rapid heat loss, danger of infection and disturbance of the systemic circulation.

The cardinal objects in the treatment of empyema are sterilization and obliteration of the cavity. Unless both of these objects are attained permanent healing does not occur.

Dakin's solution (neutral 0.5 per cent solution of sodium hypochlorite), when intelligently used, and combined with adequate drainage, is able to accomplish both of these objects simultaneously. As a decorticating agent it has proved so satisfactory that the belief seems justified that the necessity for the performance of mutilating operations of the type of Fowler-Delorme, Estlander, Schede, etc., will almost never arise, particularly in those cases which have been treated properly from the beginning.

Operations of the type of Estlander's and Schede's result in probably a permanent marked reduction in the vital capacity, besides being associated with a high immediate mortality.

A marked loss of nitrogen occurs during the acute stage of a streptococcus empyema, and, therefore, careful attention should be paid to the maintenance of the nutrition of these patients. The maintenance of an adequate supply of water is also important.

The experimental results on open pneumothorax seem to harmonize satisfactorily with the clinical findings on war wounds of the chest [1].

One can ask what there is to add. Dr Graham included all aspects of the problem of empyema, the mechanics of the lung, the nature of the exudate, the method of drainage, and chemical decortication. In the addendum he answered critics of his conclusions, pointing out that "Those who have disagreed with the principles of the theory have invariably failed to offer a constructive alternative hypothesis which is at all in accord with all the known facts concerning the action of pneumothorax." This earliest work of Evarts A. Graham set a standard that marked his other accomplishments—sound reasoning, careful evaluation, and courageous confrontation of forces opposing rational change.

Reference

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Management of Esophageal Injuries

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A multiinstitutional study of 39 esophageal injuries treated between 1982 and 1988 and a comprehensive review of the literature revealed an unacceptably high mortality rate of more than 20%. Results of the current study indicated that prompt diagnosis and aggressive surgical management of esophageal injuries could improve the outcome and lower the associated mortality. The clinical experience and literature review allowed us to elaborate caveats and principles that, if adhered to, should improve the outcome in esophageal injuries.

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Injuries to the esophagus remain a challenge to the thoracic surgeon as mortality rates of more than 20% continue to be reported. Although the cervical esophagus is the most frequently injured portion as a result of external penetrating trauma, iatrogenic perforation and spontaneous rupture occur often enough in the thoracic and abdominal portions to warrant inclusion in any discussion.

Because much has been written about esophageal injury [1–3], methods of diagnosis and treatment options should be well known to all of us, yet controversy exists as to the appropriate management of esophageal injuries [4, 5]. Part of the problem in making an early diagnosis is that esophageal perforation is not a singular entity. The patients are a heterogenous group, with perforations occurring from the cervical region to the intraabdominal esophagus. Each location of injury poses its own particular problems in diagnosis and treatment. The causes of injury also vary greatly, from instrumentation or penetrating wounds to spontaneous rupture. Proponents of prompt aggressive operative management after early diagnosis have reported marked reductions in overall mortality [1–3, 5]. Nonetheless, some clinicians who advocate nonoperative management have reported equally impressive results [4, 6, 7].

A multiinstitutional analysis of esophageal injuries occurring in the greater Delaware Valley area between 1982 and 1988 was performed, and the pertinent literature was reviewed in an attempt to organize and clarify the factors that affect the cause, diagnosis, and treatment of such injuries.

Material and Methods

A retrospective review of the charts of patients with a discharge diagnosis of esophageal perforation at five institutions* in the greater Delaware Valley area between the years 1982 and 1988 revealed 39 patients with esophageal injuries. The following data were collected: age, sex, history, physical findings, cause and site of perforation, method of diagnosis (eg, chest roentgenogram, contrast radiography, endoscopy, computed tomography, or operative exploration), treatment, and outcome. Excluded were patients with anastomotic leaks or perforations secondary to neoplasm, or those in whom the diagnosis was made on clinical grounds alone (eg, fever or leukocytosis after endoscopic procedures).

Thirty-nine patients were identified with confirmed esophageal perforation. There were 21 men and 18 women with a median age of 55 years. The most frequent cause of perforation was instrumentation. Other causes were penetrating trauma, spontaneous rupture, paraesophageal operation, foreign body, and blunt trauma (Table 1). Most perforations occurred in the thoracic esophagus; the fewest occurred in the abdominal esophagus. Seventeen of the 23 thoracic esophageal injuries were caused by instrumentation, 12 of which were sustained during therapeutic dilation and 5 of which were sustained during diagnostic endoscopy. Six were spontaneous ruptures. The abdominal esophageal injuries comprised 2 spontaneous ruptures and 1 injury from therapeutic dilation. There were 13 cervical perforations. Eight were penetrating wounds, 2 resulted from foreign bodies and 2 resulted from instrumentation; 1 blunt trauma injury occurred.

In all, there were 21 iatrogenic injuries: 2 subsequent to diagnostic endoscopy, 13 resulting from therapeutic dilation, 3 secondary to paraesophageal operation, 1 resulting from an esophageal obturator airway, 1 resulting from cricothyroidotomy, and 1 resulting from variceal sclerotherapy.

Pain was the most frequent symptom (69%), with hematemesis, dyspnea, fever, and dysphagia occurring in 8% to 33% of the patients, respectively. A penetrating wound or subcutaneous crepitus suggested the diagnosis in 18%. Diagnosis was confirmed by contrast radiography in 23 patients (60%) and by endoscopy in 5 (13%). Roentgenograms showed abnormal air in soft tissues or free air in 10 patients (25%) and pleural effusion in 8 (21%). Operation was needed to confirm the diagnosis in 6 patients (15%).

All patients received antibiotic therapy and fluid resuscitation. The mainstay of nonoperative treatment was

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* The five institutions were Thomas Jefferson University Hospital, Temple University Hospital, Hospital of the University of Pennsylvania, Albert Einstein Medical Center, Northern Division, and New Jersey College of Medicine & Dentistry (Cooper).

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Table 1. Causes of Esophageal Perforation

Cause	n	%
Instrumentation	19	49
Spontaneous rupture	7	18
Penetrating trauma	7	18
Paraesophageal operation	3	8
Foreign body	2	5
Blunt trauma	1	2
Total	39	100

broad-spectrum antibiotics, hyperalimentation, and nasogastric suction.

Cervical Esophagus

Eleven wounds in the cervical esophagus were treated with primary closure and drainage and 2 were treated nonoperatively. The only patient in this group who died had been treated operatively within 24 hours of sustaining the injury but had suffered major associated injuries.

Thoracic Esophagus

Thirteen wounds in the thoracic esophagus were treated operatively and 10 were treated nonoperatively. In the operative group, 3 simple drainages, 7 primary closures with wide mediastinal drainage, 2 exclusions and drainage, and 1 resection were performed. Patients who had severe associated disease and were not considered suitable for surgical intervention were treated with simple drainage. There were 9 deaths (39%) in this group. Only 1 death occurred in patients treated within 24 hours of injury. Eight of the 13 patients treated after 24 hours died, 4 in the operative group and 4 in the nonoperative group.

Abdominal Esophagus

All three abdominal esophageal injuries were treated with primary closure and drainage. Two patients survived. Treatment of the patient who died had been delayed for more than 24 hours. Overall mortality for the entire study group was 28% (11 deaths). Of 26 patients in whom definitive therapy was instituted within 24 hours, only 2 (8%) died, but 9 (69%) of 13 for whom treatment was delayed longer than 24 hours died (Figs 1 and 2).

The outcomes in nine reported series of esophageal injuries, including our own, are shown in Table 2. Overall mortality from esophageal perforations varied from 9% to 28%. Mortality among patients treated within 24 hours of sustaining the injury was substantially less than among those for whom diagnosis and treatment were delayed. Injuries to the cervical esophagus were associated with less mortality than were injuries to the thoracic or abdominal esophagus.

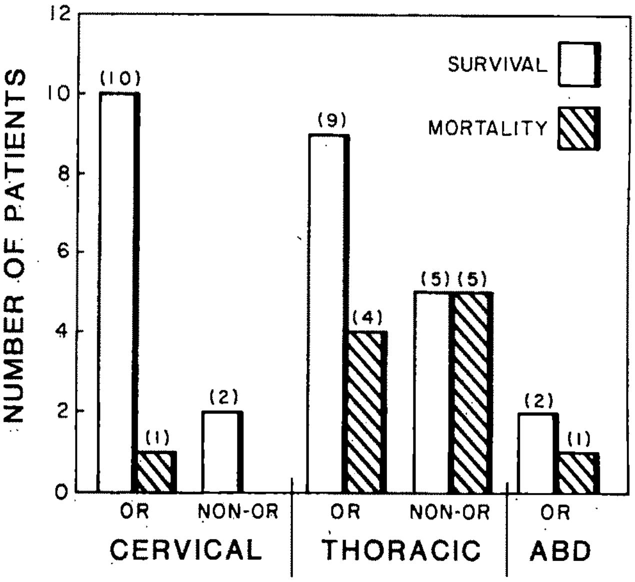

Fig 1. Outcome of esophageal injuries relative to mode of therapy, (operative [OR] or nonoperative [NON-OR]) and anatomical site.

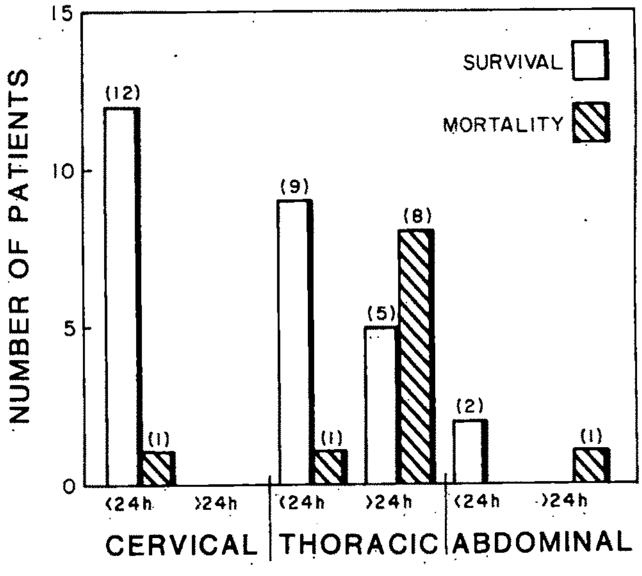

Fig 2. Outcome of esophageal injuries relative to time interval between injury and subsequent treatment (<24 h or >24 h) according to anatomical site.

Comment

The esophagus is a unique organ in the gastrointestinal tract in that it traverses three anatomical zones, namely the neck, the thorax, and the abdomen. Because in each of these areas it is in intimate contact with other vital organs, penetrating injuries rarely involve only the esophagus. Injuries to the great vessels, whether in the thorax, neck, or abdomen, increase the morbidity and mortality associated with esophageal injury. Obviously, any injury to contiguous structures such as the heart, lungs, larynx and trachea, stomach, pancreas, spleen, or spinal cord have further negative impact on outcome. In a collected series of esophageal injuries, Mulder and Barkun [15] reported mortality rates of 9% to 23%; the latter was associated with intrathoracic injuries. Even in a series of more recent esophageal injuries, a mortality rate of more than 20% was reported. Isolated injuries to the esophagus from

Table 2. Esophageal Injuries Observed and Treated in Nine Series

Author (year)	Number of Cases	Anatomical Location	Cause of Injury	Death Rate[a]		
				<24 h[b]	>24 h[b]	Combined
Bladergroen et al [1] (1937–1984)	127	37 cervical, 90 thoracic/ abdominal	70 iatrogenic, 19 spontaneous, 38 trauma/other	11/72 (15)	26/55 (47)	37/127 (29)
Cohn et al [present study] (1982–1988)	39	13 cervical, 23 thoracic, 3 abdominal	22 iatrogenic, 7 spontaneous, 10 trauma	2/25 (8)	9/14 (64)	11/29 (28)
Kostiainan et al [8] (1967–1982)	29	3 cervical, 26 thoracic/ abdominal	12 iatrogenic, 12 spontaneous, 5 foreign body	2/15 (13)	4/7 (57)	7/29[c] (24)
Larsen et al [9] (1965–1982)	57	7 cervical, 50 thoracic/ abdominal	42 iatrogenic, 26 spontaneous/ other	7/37 (19)	7/20 (35)	14/57 (25)
Larsson et al [10] (1979–1984)	23	23 thoracic	23 iatrogenic	1/20 (5)	1/3 (33)	2/23 (9)
Nesbit et al [11] (1975–1984)	51	17 cervical, 30 thoracic, 4 abdominal	23 iatrogenic, 12 spontaneous, 16 trauma	4/36 (11)	4/15 (26)	8/51 (16)
Radmark et al [12] (1972–1981)	39	1 cervical, 37 thoracic, 1 abdominal	39 iatrogenic (esophagoscopy)	. . . /32	. . . /7	7/39 (18)
Shockley et al [13] (1983–1984)	9	9 cervical	7 iatrogenic, 2 foreign body	0/6 (0)	1/3 (33)	1/9 (11)
Skinner et al [14]	47	Unspecified	26 iatrogenic, 13 neoplasm, 8 other	2/23 (9)	7/24 (29)	9/47 (19)

[a] Numbers in parentheses are percentages. [b] From time of injury to diagnosis and treatment for all injuries regardless of location. [c] The time from injury to treatment was unspecified for 7 patients.

other causes, however, have occurred in sufficient numbers to create a body of information that provides surgeons with an understanding of the seriousness of such injuries and lends direction to the diagnosis and management of them.

Cervical Esophagus

Most cervical esophageal injuries are due to the penetrating trauma of gunshot and stab wounds. Far fewer penetrating wounds in the cervical esophagus are due to instrumentation, blunt trauma, foreign bodies, or endotracheal or nasogastric intubations [16, 17]. Ordog and colleagues [18] reported injuries to the pharynx and esophagus in only 6% of 110 bullet wounds of the neck; these were primarily associated with wounds in zones II and III. Pain, dysphagia, bleeding from the mouth, and hemotemesis or hemoptysis signal penetrating esophageal injury. However, after instrumentation, pain, dysphagia, fever, and subcutaneous emphysema may herald perforation.

Soft tissue x-ray films of the neck or of the cervical spine suggest an esophageal injury if air is present in the soft tissues or if the prevertebral shadow is wide. Air in the soft tissues is occasionally misleading because injuries to the airway present a similar picture. Contrast radiography and endoscopy provide the highest diagnostic yield in such injuries. In a study by Weigelt and co-workers (Weigelt JA, Thal ER, Snyder WH, et al, unpublished observations), penetrating cervical esophageal injuries were investigated by contrast radiography, rigid endoscopy, and fiberoptic endoscopy. Eighty percent were diagnosed by contrast radiography or rigid endoscopy, and only 50% were detected by flexible endoscopy. That 20% of the lesions can be missed by all of these diagnostic techniques is of paramount importance. Chest roentgenography should always be performed in cases of injury to the cervical esophagus to rule out hemothorax or pneumothorax. Angiography may be necessary if an associated vascular injury is suspected.

Although some penetrating neck wounds can be treated nonoperatively, all esophageal and airway injuries should be managed operatively. There is nothing more devastating than "spit-fistula" contamination of a vascular suture line or an airway repair. A two-layered repair accurately approximating mucosa to mucosa and muscularis to muscularis is accomplished with 3-0 or 4-0 polyglactin or polydiozanone suture. The suture line is buttressed with a pedicle strap muscle flap, and the area is thoroughly drained. Broad-spectrum antibiotics are administered perioperatively. Occasionally, a perforation cannot be identified even with the esophagus insufflated with air under a layer of sterile water. In these instances, simple drainage and antibiotic therapy should suffice. Select patients with well-localized and contained instrumental perforations that meet the Cameron criteria [4] may be managed nonoperatively with antibiotics and hyperalimentation. However, the perforation must be well contained and drain into the esophagus, and the patient must be relatively asymptomatic with minimal signs of clinical sepsis.

Thoracic Esophagus

In injuries to the intrathoracic esophagus, instrumental perforation and spontaneous perforation remain the major causes of esophageal injury. Some are caused by foreign body penetration, paraesophageal operation, manipulation of indwelling therapeutic tubes, traumatic intubation, external penetrating wounds, variceal sclerotherapy [19, 20], and penetration due to Angelchik antireflux prosthesis [21]. Perforations of the intrathoracic esophagus are potentially lethal because they can result in extensive infection of both the mediastinum and pleural spaces with myriad organisms, including virulent anaerobic mouth organisms [3]. Decisions regarding appropriate therapy require consideration of the cause of perforation and any underlying disease process(es). All penetrating wounds of the thoracic esophagus, all spontaneous ruptures, and all perforations associated with distal esophageal obstruction must be promptly diagnosed and managed operatively. Delays in diagnosis or management are associated with pronounced increases in mortality.

A report from our institution in 1960 [22] advocated a high index of suspicion, early diagnosis, and prompt surgical intervention with primary repair and adequate drainage in an effort to reduce the morbidity and mortality associated with instrumental perforation of the esophagus. Delays in diagnosis and treatment produced greater morbidity and mortality. As a rule, perforations should be suspected in any patient who complains of persistent chest or abdominal pain after esophageal instrumentation. Contrast radiography should be performed to confirm the diagnosis. Widening of the mediastinum, pneumomediastinum, pneumothorax, or pleural effusion evident on chest roentgenogram may suggest esophageal injury. With rare exception, operative intervention should be carried out immediately after the diagnosis is established.

After the edges of the wound are freshened a two-layered repair of the perforation should be performed, with wide drainage of the mediastinum. The repair is always buttressed with a pedicle flap from adjacent pleura [23] or intercostal muscle. Any distal esophageal obstruction must be attended to appropriately. Strictures can be dilated under direct vision or opened longitudinally and closed transversely; when such strictures are associated with esophageal reflux accompanied by an antireflux procedure, the area of repair can be buttressed with a fundoplication [14]. Esophagomyotomy should be performed for achalasia, and the area of perforation should be buttressed by a Thal patch or the fundoplication of an antireflux procedure. If the distal obstruction is a tumor and contamination is not extensive, and if the condition of the patient will permit, resection and primary anastamosis is undertaken. Indwelling or fundoplication to buttress the anastamosis, or reinforcement of the anastomosis with a pleural or intercostal muscle flap, may minimize anastomotic leaks, which are associated with a high mortality.

Spontaneous perforation of the esophagus, first described by Boerhaave [24], refers to disruption of the full thickness of the esophageal wall. It is often associated with prolonged or forceful vomiting. Acute upper abdominal and thoracic pain preceded by episodic or forceful vomiting associated with mediastinal or cervical subcutaneous emphysema, or both, suggest perforation. The diagnosis can be confirmed by contrast radiography.

Nasogastric decompression, fluid resuscitation, and antibiotics are followed immediately by surgical intervention. Through a left thoracotomy, the mediastinal pleura is opened wide and the site of perforation is identified. The muscular rent should be lengthened to expose the entire mucosal tear, which is often much more extensive than the muscular tear. Failure to expose the entire rent could result in an incomplete closure of the mucosal tear, which would lead to suture line leakage [25]. The tissue edges are freshened when necessary, and a mucosa-to-mucosa and muscularis-to-muscularis two-layered closure is performed. The repair is always buttressed. The mediastinum and pleural space are thoroughly drained.

When surgical intervention is late and the tissues will not hold sutures well, a variety of surgical options are available. Wide drainage of the area alone, partial closure of the perforation over a T tube with sump drainage of the area, and exclusion with a diverting cervical esophagostomy and ligation of the distal esophagus with an absorbable suture have all been used successfully. Each procedure is supplemented by a decompressing gastrostomy and feeding jejunostomy [1–3, 19, 26, 27]. These surgical procedures are used not only for repair of spontaneous ruptures, but for repair of other esophageal injuries as well.

Operative intervention is sometimes necessary to confirm a diagnosis of penetrating wound to the intrathoracic esophagus when the location of a foreign body or the course taken by a missile suggests an esophageal injury that cannot be detected by either contrast radiography or endoscopy. If associated injuries require an anterior approach through which the esophageal perforation cannot be repaired effectively, repairs to adjacent organs should be carried out and the patient turned over to approach the esophageal injury posterolaterally using the standard principles of esophageal repair (K. L. Matton, personal communication, May 1988). Nonoperative management may be appropriate in select cases of instrumental perforation of the thoracic esophagus that meet Cameron's criteria. However, one must keep in mind that delays in management are associated with an increase in mortality and greater technical difficulty in managing the offending pathology. Distinguishing between an early contained esophageal injury and one that will cause extensive mediastinal contamination is sometimes extremely difficult.

Abdominal Esophagus

The intraabdominal esophagus can rupture spontaneously, or it can be perforated by endoscopic manipulation or penetrating injuries; it can also be ruptured by paraesophageal operations such as vagotomy, antireflux procedures, or hiatal hernia repair. Epigastric pain with signs of peritoneal irritation signal perforation. Free air under the diaphragm may be evident on an erect chest radiogram, and perforation can be confirmed by contrast radiography. The previously stated principles of repair apply, and a successful outcome can be achieved by a two-layered closure buttressed by fundoplication or an omental wrap coupled with decompressing gastrostomy and feeding jejunostomy. Morbidity and mortality are greatly influenced by associated injuries to the liver, spleen, major vessels, or pancreas.

Caustic injuries of the esophagus occur mostly in children and are caused by ingestion of strong acids or alkalis. Industrial strength alkalis usually affect the esophagus, whereas strong acids affect the stomach. Endoscopy within the first 24 hours is performed to assess the extent of the injury and to determine its severity. Industrial strength lye always causes severe injuries, usually circumferential and associated with white patchy eschar. Stricture formation and the need for esophageal replacement are determined by the depth of the burn. Steroids have been ineffectual in altering the course of these burns [28]. A baseline barium swallow should be obtained.

The objective of therapy is to restore normal swallowing function. If the burn is severe, a gastrostomy should be performed, and the patient should be instructed to swallow a string as a guide for subsequent dilations. If the burn is mild, endoscopy is repeated after 3 weeks to reassess healing or stricture formation. If the burn is moderate, or if a stricture develops, antegrade dilations are necessary at periodic intervals for up to a year. If antegrade dilation fails, or if the burn or stricture is severe, retrograde dilation with Horst dilators should be attempted every ten days to 2 weeks. If this procedure is effective, antegrade dilation can be started in 3 to 6 months and the gastrostomy closed. If retrograde dilation proves ineffective, esophageal replacement with either colon, stomach, or a reversed gastric tube should be considered.

Conclusions

Certain caveats and principles related to esophageal injuries have evolved from our experience and from the wealth of information available in the surgical literature. Most penetrating esophageal wounds occur in the neck. Perforations in the cervical esophagus have low morbidity and mortality if treated within the first 24 hours [11, 14, 29]. Most instrumental and spontaneous perforations occur within the thoracic esophagus. Instrumental perforations result more often from therapeutic dilation than from diagnostic endoscopy [30]. When pain or fever develops, either with or without subcutaneous emphysema, after instrumentation, perforation should be suspected [31]. The diagnosis can often be confirmed by contrast radiography using Gastrografin or barium sulfate [29]. The associated morbidity and mortality arise from the overwhelming sepsis caused by the myriad aerobes and anaerobes that contaminate the periesophageal region. Spontaneous perforations result in higher mortality than do instrumental perforations [10, 25, 27, 32].

Prompt recognition of the esophageal injury followed by surgical repair is the preferred method of treatment and produces the most favorable outcome. Operative procedures vary with the location and type of injury.

Drainage alone, primary repair and drainage, repair either with or without resection of the offending pathology with restoration of gastrointestinal continuity, and exclusion with or without resection are among the treatment options. Buttressing of the repaired perforation with viable tissue appears to improve the outcome. Delays in treatment are associated with an unacceptable mortality rate. Multiple operations needed to manage complications also increase mortality. Nonoperative management appears to be applicable to only a small, select group of patients who manifest no clinical signs of sepsis and have minimal, well-contained injuries.

We gratefully acknowledge the cooperation of Robert G. Somers, MD, Albert Einstein Medical Center, Northern Division; Rudolph Camishon, MD, UMDNJ-Robert Wood Johnson Medical School at Camden; Clyde Barker, MD, Hospital of the University of Pennsylvania; and Wallace Ritchie, MD, Temple University Hospital, for assistance in accessing the data used in this article.

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CORRESPONDENCE

Management of Difficult Sternal Closure After Sternal Infection

To the Editor:

In spite of antibiotics and good surgical technique, sternal infection occurs in a small proportion of patients undergoing coronary operations. The incidence of infection with the use of bilateral mammary arteries for coronary bypass grafting has been reported to be as high as 8.5% [1] and as low as 1.6% to 4.0% [2, 3].

In those situations in which infection occurs in the superficial soft tissues only and has not resulted in serious destruction or fracture of the sternum, primary closure with wire in a routine fashion can often be performed after a limited period of open drainage. At the time of closure mediastinal tissues are closely adherent to the underside of the sternum and there is no distinct surgical plane. In this setting, difficulties can be encountered in placing wires in or around the sternum to obtain secure and safe closure. Saphenous veins and mammary arteries are at risk of being damaged because dissection under the sternal halves can be tedious and hazardous. The exact location of these conduits is unknown without repeat angiography.

We have recently had the unfortunate experience of reclosing a patient's sternum because of nonunion and inadvertently placing the sternal wire around the left internal mammary artery graft. This was not suspected or discovered at operation and resulted in the patient's death several hours later. This was verified at autopsy.

We subsequently encountered a patient with a superficial wound infection after coronary bypass grafting with bilateral internal mammary arteries. There was no destruction or involvement of the sternum or mediastinum. He was treated by reopening of the wound, removal of all sternal wires, wet to dry dressings, and antibiotic therapy. Sixteen days later, after resolution of local signs and symptoms of infection, the patient's wound was closed utilizing a new technique.

No attempt was made to mobilize soft tissues on the underside of either sternal half. The sternal wire was brought down at 90 degrees to the outer table of the sternum, and the wire was brought out straight through the marrow just superior to the inner table (Fig 1). The needle was then advanced through the marrow on the opposite side just above the inner table, keeping the curve of the needle parallel to the inner table. In this manner all wires passed anterior to the inner table of the sternum, thereby avoiding all grafts. The sternum was then approximated by the application of pressure to both sides of the chest by the surgeon and assistant. When the edges were approximated, the wires were twisted and secured.

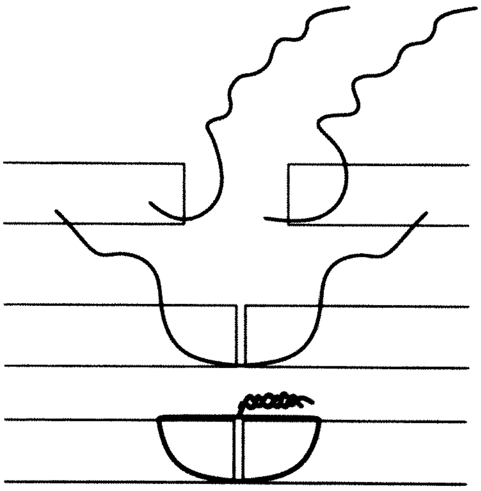

Fig 1. Method of insertion of sternal wires avoiding underlying grafts.

The wound healed promptly with no evidence of sternal instability or residual infection. Six months later the wound is healed and the sternum is solid. The patient has recently undergone an uneventful transurethral resection of the prostate.

As this technique obviously does not encompass as much bony mass as the usual wire closure, we would suggest that certain criteria be met before use. The sternal edges must be no more than one half to three quarters of an inch apart initially, and the integrity of the sternum must be well maintained with no major fracture or instability of either sternal half. This technique obviously would not be suitable if any destruction or fracture of the sternum has occurred, in which case the use of vascularized pedicle flaps might be more appropriate [4].

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Ectopic Ossification After Median Sternotomy

To the Editor:

Over a span of 11 years, during which we have performed over 4,000 heart operations through a median sternotomy, we have encountered 4 cases of ectopic ossification extending from the xiphoid into the fascia of the rectus abdominis. We have been

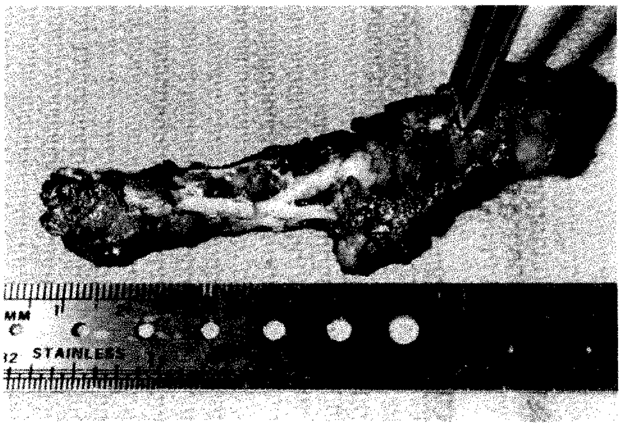

Fig 1. (Patient 1.) Excised specimen of ectopic ossification.

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Table 1. Ectopic Ossification Findings

Patient No.	Age (yr)	Sex	Operation	Symptoms	Physical Examination	Pathology	Operation to Ossification[a] (mo)	Ossification to Excision (mo)	Result
1	60	M	CABG	Epigastric pain, bending	6-cm bony mass from xiphoid caudally	4 × 11.5-cm ectopic bone	2	14	No recurrence, 6 yr
2	60	M	CABG	Epigastric pain, worse bending	Bony epigastric mass	3 × 7-cm ectopic bone	11	0	Recurrence, 13 days, but softer and no further change at 8 yr
3	48	M	CABG, LVA, endocardial excision	Epigastric pain, worse bending	Bony epigastric mass, xiphoid nearly to umbilicus	2 × 6-cm ectopic bone	1	17	No recurrence at 18 mo
4	30	F	Median sternotomy, laparotomy for liver rupture	Epigastric pain, worse bending	Bony mass, xiphoid nearly to pubis	6 × 30-cm ectopic bone	8	5	No recurrence at 18 mo; continued growth from time noted to excision

[a] Time patient first noticed the ectopic ossification.

CABG = coronary artery bypass grafting; LVA = left ventricular aneurysmectomy.

unable to find a description of this phenomenon after median sternotomies.

The following case illustrates the findings. A 60-year-old man had elective aortocoronary saphenous vein revascularization in 1977 via a median sternotomy. Two months later, he noted a painful epigastric mass attached to the xiphoid. Bending forward exacerbated the pain. Fifteen months after the operation, examination disclosed a 6-cm hard mass fixed to and extending caudally from the xiphoid midway to the umbilicus. At the time of excision, a cratered, crevassed, markedly irregular piece of new bone was excised (Fig 1). It was 11.5 cm long, and tapered from 4 cm to 0.6 cm wide. The ectopic bone lay in the fascia of the rectus abdominis and was limited to the length of the epigastric extension of the old incision. When the patient died in 1985, the mass had not recurred.

Two other patients had similar formation of ectopic ossification after coronary revascularization with saphenous vein. One of these patients had recurrence of the mass within 2 weeks of its excision! The fourth patient had a long incision beginning with a median sternotomy and ending at the pubis for the emergency treatment of massive abdominal and chest trauma. Her ectopic ossification extended from xiphoid to pubis. All 4 patients had in common a longer than usual extension of the median sternotomy into the abdomen. Three of the 4 patients had no recurrence after excision. Table 1 summarizes these cases.

Ectopic ossification has been described in a number of situations: after traumatic paraplegia [1], after hip arthroplasties [2–4], and occasionally in laparotomy scars [5–8]. In these laparotomy scars, 95% of the new bones extended from the xiphoid, and none have been reported in transverse incisions. Other peculiar forms of posttraumatic ectopic ossification have been described [9] and include Prussian's or rider's bone (adductor longus calcification from horse riding), cavalry bone (in the outer thigh from the bruising of scabbards), drill bones (deltoid or pectoral ossification from rifle recoil), gastrocnemius ossification in ballet dancers, and the self-explanatory seamstress's bottom. In all cases, the new bone has been benign.

The cause of this malady is unknown. Two causal theories suggested are injury to the xiphoid with seeding of periosteal or perichondrial cells in the incision and metaplasia of multipotent connective tissue cells to osteogenic cells. As the new bone formation has been confined to the abdominal extension of the median sternotomy, limiting this extension should limit or eliminate symptomatic ectopic ossification after median sternotomies.

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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Third Annual Meeting of the European Society for Vascular Surgery, Malmö, Sweden—September 3–5, 1989

A satellite symposium on pharmacological intervention to increase patency in arterial reconstructions will be held in the same location on September 6–7, 1989. For information on both symposia, contact the Congress Organisation Bureau, ESVS 89, c/o ICM AB, Geijersgatan 50, S-216 19 Malmö, Sweden.

Nineteenth World Congress of The International Society for Cardiovascular Surgery, Toronto, Ontario, Canada—September 5–9, 1989

For information on this meeting, contact XIX World Congress, ISCVS Administrative Offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330.

Fourth World Congress of the International Society for Diseases of the Esophagus, Chicago, Illinois—September 6–8, 1989

This meeting is sponsored by the American College of Chest Physicians and Smith Kline & French Laboratories and is accredited for hour-to-hour credit in category 1 of the Physician's Recognition Award of the AMA. For information, contact the American College of Chest Physicians, PO Box 93826, Chicago, IL 60673.

The Third Current Controversies & Techniques in Congenital Heart Surgery, Baltimore, Maryland—September 8–9, 1989

Sponsored by the University of Nebraska Medical Center. For information on this meeting, contact Terry Slade Young, Current Controversies and Techniques in Congenital Heart Surgery, 11 S Paca St, University Square Bldg, Suite 304, Baltimore, MD 21201; or telephone (301) 328-2399 (facsimile: (301) 328-8514).

Twenty-fifth Annual Meeting of The Society of Thoracic Surgeons, Baltimore, Maryland—September 11–13, 1989

For information on this meeting, contact George C. Kaiser, MD, The Society of Thoracic Surgeons, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Thirty-eighth Annual Meeting of The Scandanavian Association for Thoracic and Cardiovascular Surgery and The Scandanavian Society for Extracorporeal Technology, Aarhus, Denmark—September 13–16, 1989

For information on this meeting, contact the Secretary of the Congress Committee SATCVS/SCANSECT, Chr. Mouritzen, MD, Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus-Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

Third Annual Meeting of the European Association for Cardio-Thoracic Surgery, Munich, Federal Republic of Germany—October 9–11, 1989

For information on this meeting, contact Organizing Secretariat, Interplan Convention and Visitor Service, Sophienstrasse 1, D-8000 Munich 2, FRG; or telephone 089 59 44 92 (telex: 523183 iplan d; facsimile: 089 59 16 10).

Sixth World Congress of Bronchoesophagology, Tokyo, Japan—October 15–18, 1989

This meeting is sponsored by the Organizing Committee of the Sixth World Congress of Bronchoesophagology, the Japan Broncho-esophagological Society, and the Foundation for Advancement of International Science under the auspices of the International Bronchoesophagological Society. For information, contact the Secretariat of the Sixth

World Congress of Bronchoesophagology, c/o Japan Convention Services, Inc, Press Center Bldg, 2-2-1 Uchisaiwaicho, Chiyoda-ku, Tokyo 100, Japan; or telephone 03-508-1213 (telex: J33104; facsimile: 03-508-0820).

American College of Surgeons, Atlanta, Georgia—October 15–20, 1989

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050.

Sixteenth World Congress on Diseases of the Chest and the Fifty-fifth Annual Scientific Assembly, American College of Chest Physicians, Boston, Massachusetts—

October 30–November 3, 1989

This meeting is sponsored by the American College of Chest Physicians and the International Academy of Chest Physicians and Surgeons. For information, contact the American College of Chest Physicians, 911 Busse Highway, Park Ridge, IL 60068; or telephone (312) 698-2200.

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association, Scottsdale, Arizona—November 9–11, 1989

For information on this meeting, contact Gordon F. Murray, MD, Southern Thoracic Surgical Association, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Sixty-second Scientific Session of the American Heart Association, New Orleans, Louisiana—November 13–16, 1989

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 750-5300.

Twenty-fifth Anniversary—Open Heart Surgery, Jerusalem, Israel—December 28, 1989–January 1, 1990

For information on this meeting, contact Joseph B. Borman, MD, or the Secretariat, PO Box 32390, Jerusalem 91323, Israel; or telephone 972-2-663171 (telex: 26205 TRGBL IL; facsimile: 972-2-665277).

Specialty Review in Thoracic Surgery, Chicago, Illinois—January 8–13, 1990

This course is sponsored by the Cook County Graduate School of Medicine and is accredited for approximately 47 hours in category 1 of the Physician's Recognition Award of the AMA. For information, contact the Registrar's office: within Illinois, 1 (800) 621-4649; outside Illinois, 1 (800) 621-4651.

Twenty-seventh Annual Seminar—Coronary Atherosclerosis: New Diagnostic and Therapeutic Approaches, Orlando, Florida—January 28–February 1, 1990.

This seminar is sponsored by the Departments of Radiology and Cardiology, Mount Sinai Medical Center of Greater Miami, Miami Beach, FL, and is accredited for 20.5 hours in category 1 of the Physician's Recognition Award of the AMA. For information on this meeting, contact Lucy R. Kelley, Program Coordinator, Radiology Seminars, Inc, PO Box 143762, Coral Gables, FL 33114-3762; or telephone (305) 674–2810.

Nineteenth Annual Meeting of the German Society for Thoracic, Cardiac, and Vascular Surgery, Bad Nauheim, Federal Republic of Germany—February 22–24, 1990

For information on this meeting, contact Hagen D. Schulte, MD, Professor of Surgery, Department of Thoracic and Cardiovascular Surgery, Heinrich-Heine-University, Moorenstrasse 5, D-4000 Dusseldorf, Federal Republic of Germany.

Aortic Surgery Symposium II, New York, New York—May 4–5, 1990

This symposium is sponsored by Meadox Medicals, Inc, and is accredited for 15 hours in category 1 of the Physician's Recognition Award of the AMA and toward the New York Medical Association Certificate in Continuing Medical Education. For information, contact Beverly Farrier, Symposium Coordinator, ProMedica International, 620 Newport Center Drive, Suite 575, Newport Beach, CA 92660.

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

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Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae and names of references.

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Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland, OR 97213-2282. 124C/I

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV.

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Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits. Respond with curriculum vitae.

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Cardiothoracic surgeon: Board certified or eligible is sought to join an academic practice in the Midwest. Opportunity to become active and contribute to a growing cardiothoracic transplantation program. Excellent research opportunities available.

Direct curriculum vitae or inquiries to J. Terrance Davis, MD, Medical College of Ohio, C.S. #10008, Toledo, OH 43699. An equal opportunity employer. 153F/I

Cardiovascular and thoracic surgeon, BE/BC, wanted to join a busy private practice in Pittsburgh, PA. Please respond with curriculum vitae and details of experience.

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Cardiothoracic/vascular surgeon wanted to join established practice in Ohio. Recent graduate preferred. Please submit curriculum vitae and three references.

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Cardiac surgeon needed for growing open heart program. Our service area encompasses more than 200,000 people in the intermountain West. Our program offers an extremely modern practice in Idaho's newest and largest referral center. Commutes average 10 minutes on uncrowded country roads. Recreation opportunities include some of the Rockies' finest skiing, hunting, fishing, camping, and hiking. For the right board eligible/certified cardiovascular surgeon, this position combines a fully supported cardiac practice with big country living.

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Thoracic surgeon: Board certified or eligible. Interested in practice of thoracic, vascular, and general surgery in the greater Cincinnati area. Send resume.

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Additional cardiothoracic surgeon, BC/BE, to join expanding practice of cardiac/thoracic surgery at 500-bed affiliate of major medical center in Midwest. Skills in internal mammary grafting, valve repair, ventricular assist important, and familiarity with electrophysiological procedures desired. Excellent investigational facilities available with ample opportunity for clinical or basic science research. Private practice with academic affiliation—solid general surgery residency with active medical student participation. Salaried position leading to eventual partnership for the right individual. Send CV.

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Send CV to Roger Ecker, MD, 365 Hawthorne Ave, Suite 301, Oakland, CA 94609. 181HI

Assistant surgeon—Preferably experienced in cardiothoracic surgery to first assist in the operating room. Active adult and pediatric cardiovascular surgery practice in metropolitan DC area. Practice includes arrhythmia and vascular surgery, and cardiac transplantation.

Please respond with curriculum vitae outlining training and recent surgical experience to Virginia Heart Surgery Associates, 3301 Woodburn Road, Suite 301, Annandale, VA 22003. 183H/J

Cardiothoracic surgeon: Private practice position, Great Lakes, adult cardiothoracic and vascular surgery. Must be currently active in cardiac surgery. Send CV and references.

Please respond to Box 184. 184HI

Cardiovascular/thoracic surgeon, BC/BE, needed to join busy expanding private practice in Colorado Springs. Adult and pediatric cardiothoracic and some vascular. Initial contact should include curriculum vitae and references.

Please send CV and three reference letters to E. S. Yee, MD, Director of Cardiovascular Surgery, 1725 E Boulder St, Suite 104, Colorado Springs, CO 80909. 185H/J

Chairperson, Department of Thoracic-Cardiovascular Surgery. Winthrop-University Hospital, a 533-bed tertiary care hospital of SUNY Stony Brook, is seeking candidates to chair its Cardiothoracic Department. Applicants should have strong clinical, teaching, and administrative skills, as well as a commitment to research. The department conducts a fully approved open heart program and performs a large volume of thoracic and vascular surgery. The hospital will support a fellowship program and research activities.

Send CV to Alan Fein, MD, Chairman, TCV Search Committee, Winthrop-University Hospital, c/o 222 Station Plaza No., Suite 400, Mineola, NY 11501. 186H/J

Cardiothoracic/vascular surgeons: St. Francis Hospital—The Heart Center—a 227-bed teaching center, is the only designated cardiac specialty hospital in NY State. We are seeking cardiothoracic and vascular surgeons (2) to join a geographic full-time private group providing surgical assistance. Reimbursement is to be on a modified fee-for-service basis. Successful candidates will be expected to assist on approximately 350 open heart cases per year and share responsibility for ICU coverage.

For immediate consideration, send CV to William J. Noble, MD, or Norman B. Thompson, MD, St. Francis Hospital, 100 Port Washington Blvd, Roslyn, NY 11576. An equal opportunity employer. 187H

Cardiothoracic surgeon, board certified or eligible, wanted to join established 5-man practice. Experience required in transplantation, adult cardiac surgery, and thoracic surgery. Northwest city with easy lifestyle and outdoor activities. Salary leading to partnership.

Please respond to Box 188. 188H/J

Cardiothoracic surgeon wanted for a busy, expanding, 3-man, private practice group in the Midwest. Applicant must be ABTS eligible or certified. Prefer recent graduate with some background in electrophysiologic surgery. Please send curriculum vitae.

Please respond to Box 189. 189H/A

Cardiac surgeon urgently needed for 2-year old practice in Northwest. Very early parity in case distribution, salary, and partnership. Board eligible-certified candidates submit curriculum vitae and references.

Please respond to Box 190. 190HI

Cardiovascular and thoracic surgeon wanted for growing practice in the Southwest. Applicant must be ABTS eligible or certified. Send curriculum vitae.

Please respond to Box 193. 193H

Cardiovascular and thoracic surgeon: Position available for a board certified or eligible cardiovascular and thoracic surgeon to join a 3-man private practice involved with adult cardiac, thoracic, and peripheral vascular surgery in a desirable eastern metropolitan area. Association will lead to competitive salary, excellent fringe benefits, and early partnership. Please send curriculum vitae.

Please respond to Box 192. 192H/K

Cardiovascular physician assistant needed for growing cardiac surgical practice in Northwest. Competitive salary, privileges, and call schedule to allow advantage of excellent geographic location.

Please respond to Box 191. 191HI

Three-man group currently performing adult cardiac, thoracic, and vascular surgery in desirable northeast location. Seeking associate leading to partnership. Candidate must be BC/BE.

Please respond to Box 194. 194H/J

SITUATIONS WANTED

Cardiovascular and thoracic surgeon wishes to relocate. University trained with ABTS certification. Ten years' experience with extensive cardiac, thoracic, and peripheral vascular surgery. Would be interested in starting new program or association with group. Curriculum vitae and references available upon request.

Please respond to Box 117. 117C/H

Cardiovascular and thoracic surgeon, 37, ABS, ABTS, personable, strong technical skills and patient care, interested in joining group or starting new program.

Please respond to Box 133. 133E/H

Cardiovascular and thoracic surgeon wishes to relocate. ABS, ABTS with 10 years experience in adult cardiac, thoracic, and peripheral vascular surgery. All areas considered. Willing to initiate or help initiate new program.

Please respond to Box 136. 136E/H

Cardiovascular and thoracic surgeon, 42, American, ABS, ABTS, ABVS. Eight years private practice experience. Completed overseas fellowship in heart and heart/lung transplantation. Seeks opportunity with individual or group practice of cardiovascular and thoracic surgery. Curriculum vitae and references upon request.

Please respond to Box 199. 199G/I

FELLOWSHIPS

Fellowship in thoracic and cardiovascular surgery at Baylor University Medical Center.

Contact Dr Harold C. Urschel, 3600 Gaston Avenue, Suite 1201, Dallas, TX 75246; telephone (214) 824-2503. 129G/L

Physicians—Cardiothoracic fellowships available immediately; for cardiac center located on the north shore of Long Island with a busy program in adult and pediatric cardiac surgery. Opportunity for outstanding candidates at conclusion of fellowship to join full-time private practice associate group specializing in cardiac surgery. Applicants must have completed training in general surgery with special interest and/or training in cardiothoracic surgery. Salary commensurate with qualifications; excellent fringe benefits.

Resumes and references should be forwarded to Coordinator, Medical Staff Affairs, St. Francis Hospital, 100 Port Washington Blvd, Roslyn, NY 11576. An equal opportunity employer. 158F/H

Vascular surgeon fellow: Deborah Heart & Lung Center is currently seeking qualified physician for fellowship training or surgical rotations in adult vascular surgery. Outstanding educational opportunities with excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart & Lung Center, Browns Mills, NJ 08015; (609) 893-6611, Ext 634. 175G/I

Surgical fellow—Clinical fellowship position available in adult and pediatric cardiothoracic surgery. Large volume of cases. NJ license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Department of Surgery, Deborah Heart & Lung Center, Browns Mills, NJ 08015. 167G/L

Pediatric cardiovascular fellowship position available 7/89 for board credit at Children's Hospital of New Jersey for 4 months. Must have New Jersey license.

Contact Joseph J. Amato, MD, Director, Department of Pediatric Cardiovascular Surgery, Children's Hospital of New Jersey (UHMC), 15 South Ninth St, Newark, NJ 07107; (201) 268-8606. 179GH

Cardiac Surgery Fellow—Clinical position for 1 or 2 years in very busy private practice in northern Virginia doing adult cardiac, thoracic, and vascular surgery, pediatric cardiac surgery, and cardiac transplantation. Responsibilities include perioperative care on surgical floor and intensive care unit and first assisting in surgery. Ideal position for resident having completed general surgery and waiting for cardiothoracic training program. Excellent salary and benefits. ABS eligible or certified.

Please respond with curriculum vitae with a description of personal interests and career goals to Virginia Heart Surgery Associates, 3301 Woodburn Road, Suite 301, Annandale, VA 22003. 182H/J

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The Pharmacological Treatment of Cardiovascular Diseases

Edited by
John B. Kostis, M.D., Professor of Medicine and Chief, Division of Cardiovascular Diseases and Hypertension, UMDNJ-Rutgers Medical School, New Brunswick, New Jersey
Eugene A. DeFelice, M.D., Clinical Professor of Medicine, Division of Cardiovascular Diseases and Hypertension, UMDNJ-Rutgers Medical School, New Brunswick, New Jersey

This brand new volume presents a complete survey of the pharmacological treatment of cardiovascular diseases. Comprehensive descriptions of the manifestations of a wide range of cardiovascular diseases and their pathophysiology are detailed in this 408 page, 22 chapter text. Highlighted are all aspects of those disorders most commonly encountered in clinical practice and the appropriate pharmacologic agents needed for effective treatment.

The text is divided into sections that provide in-depth coverage of the following topics:

- Hypertension
- Angina Pectoris
- Arrhythmias
- Heart Failure
- Myocardial Infarction

The Pharmacological Treatment of Cardiovascular Diseases also contains these useful features:

- Summary tables showing drug comparisons, their efficacy, and adverse reactions
- Reference lists at the end of each chapter that provide information for further study

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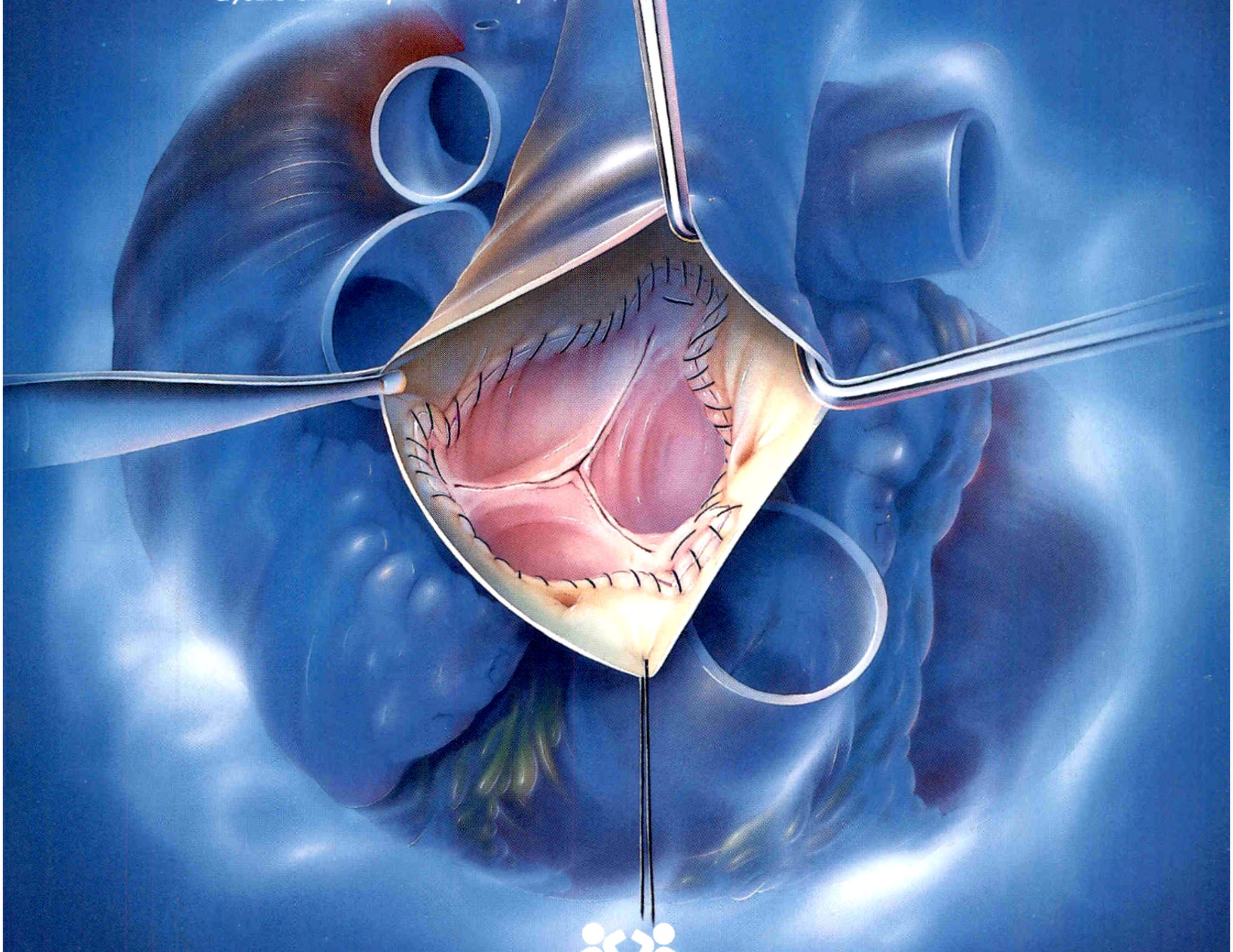

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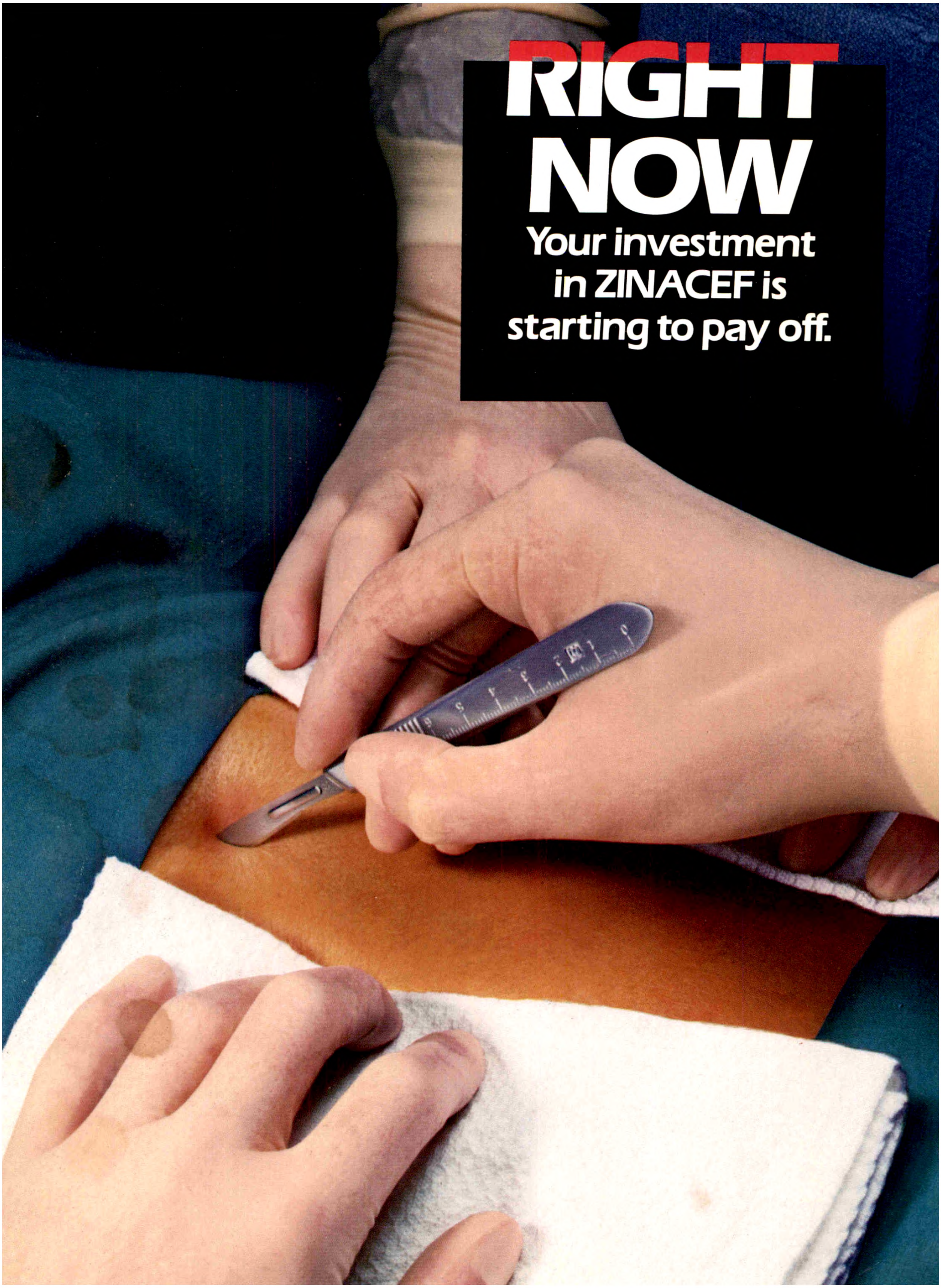
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In a recent study, ZINACEF was shown to be "significantly more effective...than cefazolin in preventing postoperative wound infections following open-heart surgery"[1]—especially against *Staphylococcus aureus* and *S epidermidis.*

Reduces postoperative complications—infectious and financial

A recent nationwide analysis revealed that each postoperative wound infection represents a nonreimbursable loss to a hospital of $2,467, on average.[2] By reducing the rate of infection, ZINACEF can help reduce these losses.

1. Slama TG, Sklar SJ, Misinski J, et al: Randomized comparison of cefamandole, cefazolin, and cefuroxime prophylaxis in open-heart surgery. *Antimicrob Agents Chemother* 1986;29:744-747.
2. Haley RW, White JW, Culver DH, et al: The financial incentive for hospitals to prevent nosocomial infections under the prospective payment system. *JAMA* 1987;257:1611-1614.

Please consult Brief Summary of Prescribing Information on next page before prescribing or administering ZINACEF.

Glaxo Glaxo Inc., Research Triangle Park, NC 27709

ZINACEF® IM/IV **GLAXO**

sterile cefuroxime sodium

Brief summary. Before prescribing, consult complete Prescribing Information.

INDICATIONS AND USAGE: ZINACEF® is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *S pneumoniae* (formerly *D pneumoniae*), *H influenzae* (including ampicillin-resistant strains), *Klebsiella* sp, *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, and *E coli*.
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* sp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* sp, and *Enterobacter* sp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae* (including ampicillin-resistant strains), and *Klebsiella* sp.
5. **Meningitis** caused by *S pneumoniae*, *H influenzae* (including ampicillin-resistant strains), *N meningitidis*, and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *N gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *S aureus* (including penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. ZINACEF has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to ZINACEF.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, ZINACEF may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention: The preoperative prophylactic administration of ZINACEF may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (eg, vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. ZINACEF® (sterile cefuroxime sodium, Glaxo) should usually be given one-half to one hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of ZINACEF has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that ZINACEF therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS: ZINACEF® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH ZINACEF® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO ZINACEF OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *C difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: Although ZINACEF® rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of ZINACEF should be reduced in patients with transient or persistent renal insufficiency because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of ZINACEF may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Interference with Laboratory Tests: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (eg, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving ZINACEF.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Since ZINACEF is excreted in human milk, caution should be exercised when ZINACEF is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS: ZINACEF® is generally well tolerated. The most common adverse effects have been local reactions following intravenous administration. Other adverse reactions have been encountered only rarely.

Local Reactions: Thrombophlebitis has occurred with intravenous administration in 1 in 60 patients.

Gastrointestinal: Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Hypersensitivity Reactions: Hypersensitivity reactions have been reported in less than 1% of the patients treated with ZINACEF and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in less than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome have occurred.

Blood: A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (less than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence was seen with other cephalosporins used in controlled studies.

Hepatic: Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney: Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

HOW SUPPLIED ZINACEF® is a dry, white to off-white powder supplied in vials and infusion packs.

Each vial contains cefuroxime sodium equivalent to 750 mg, 1.5 g, or 7.5 g of cefuroxime. ZINACEF in the dry state should be stored between 15° to 30° C (59° to 86° F), and protected from light.

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NDC 0173-0354-35	1.5-g Vials (Tray of 25)
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NDC 0173-0400-00	7.5-g Pharmacy Bulk Package (Tray of 6)

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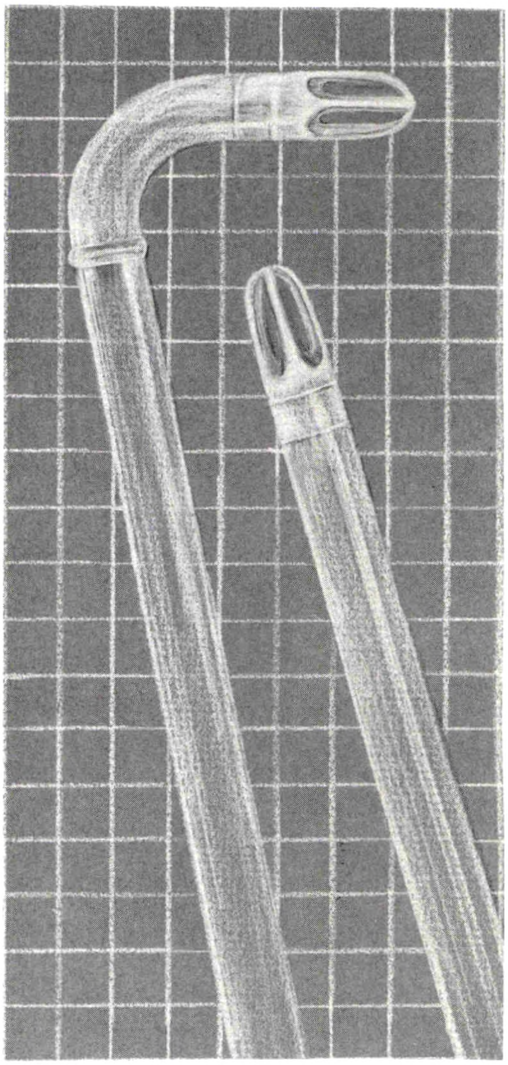

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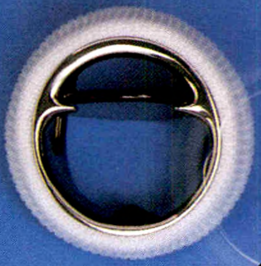

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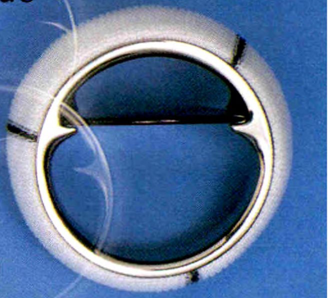

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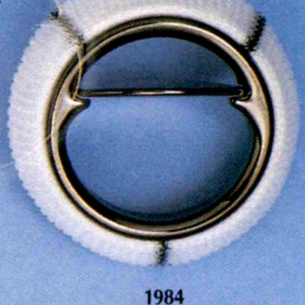

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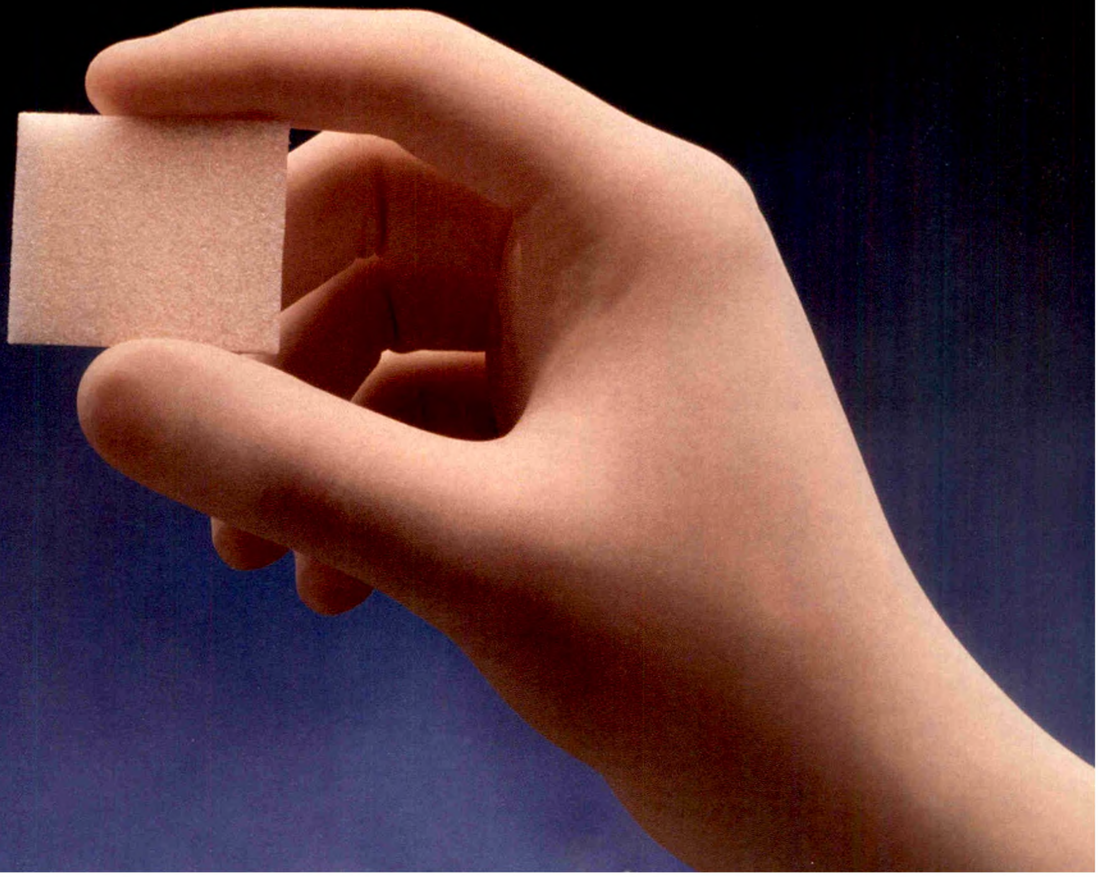

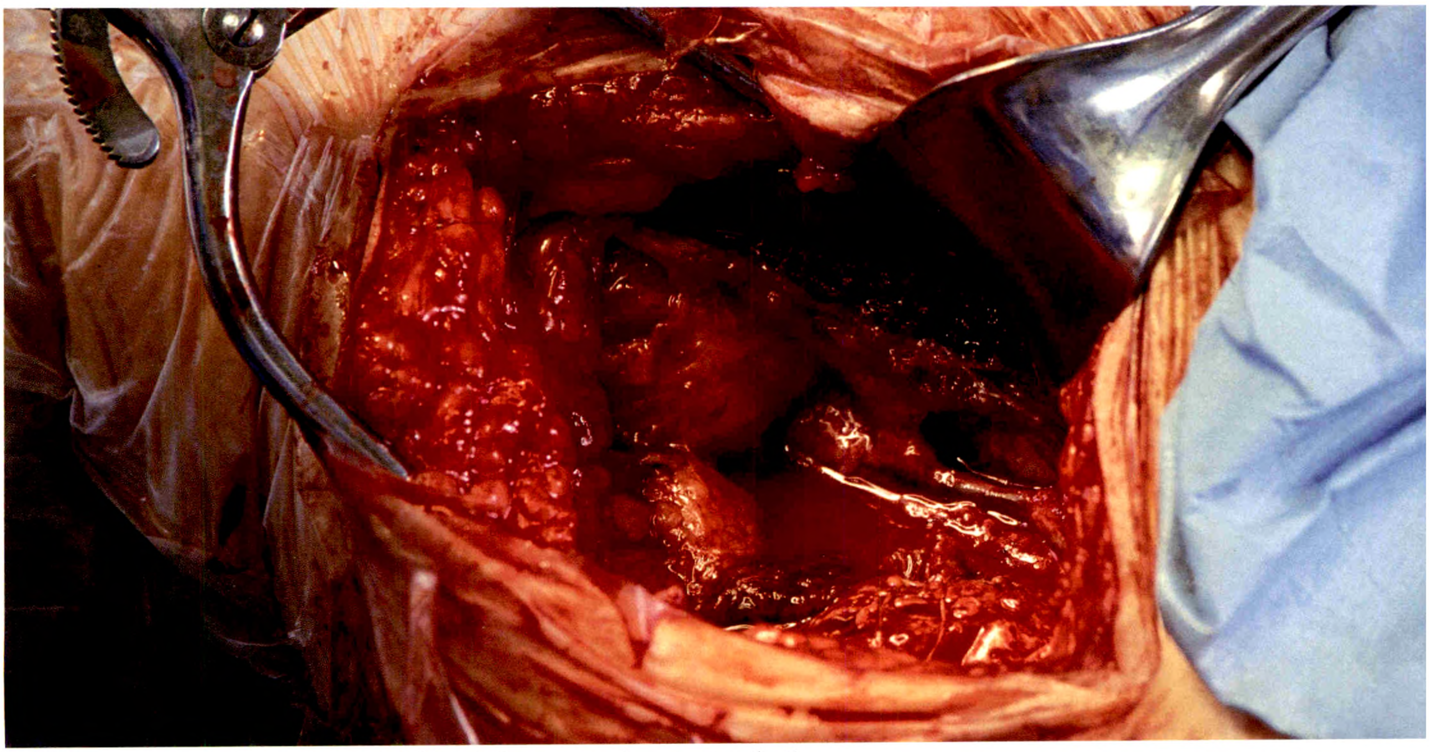

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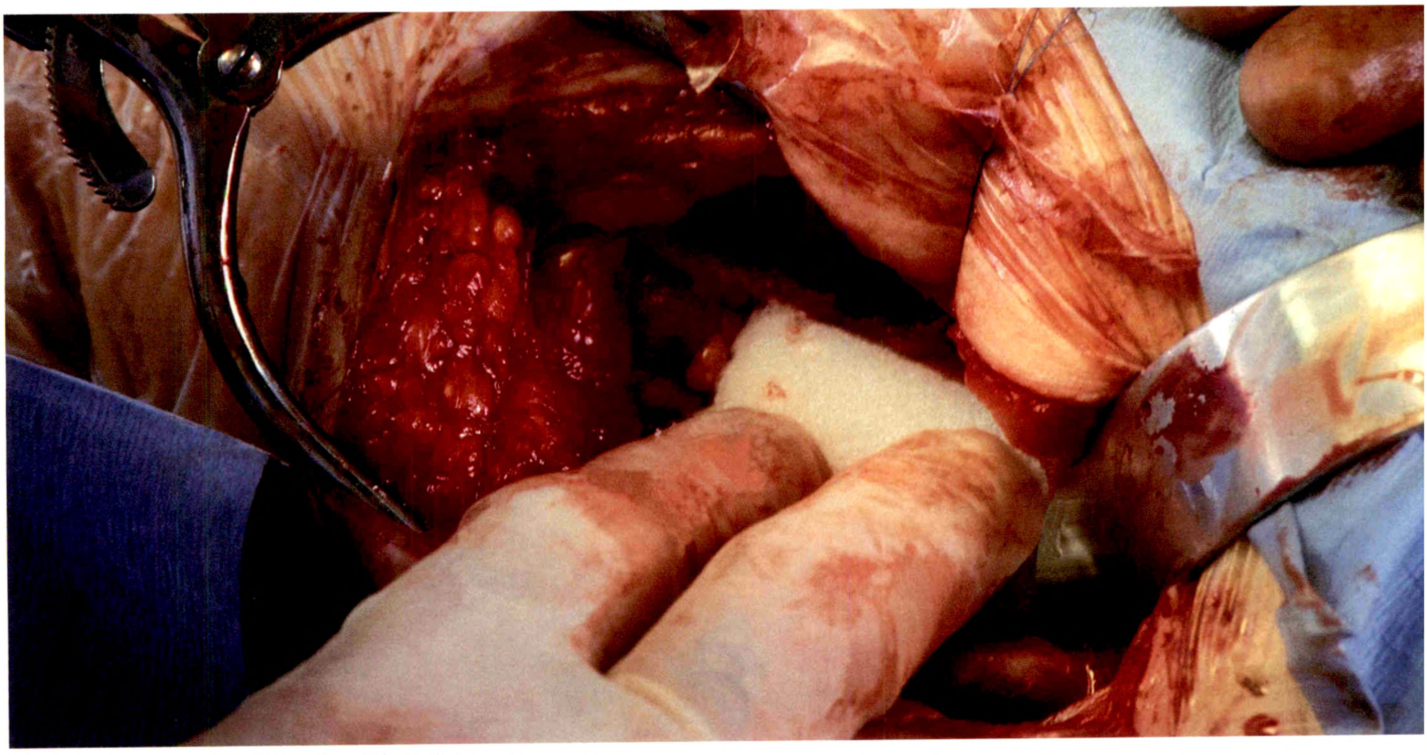

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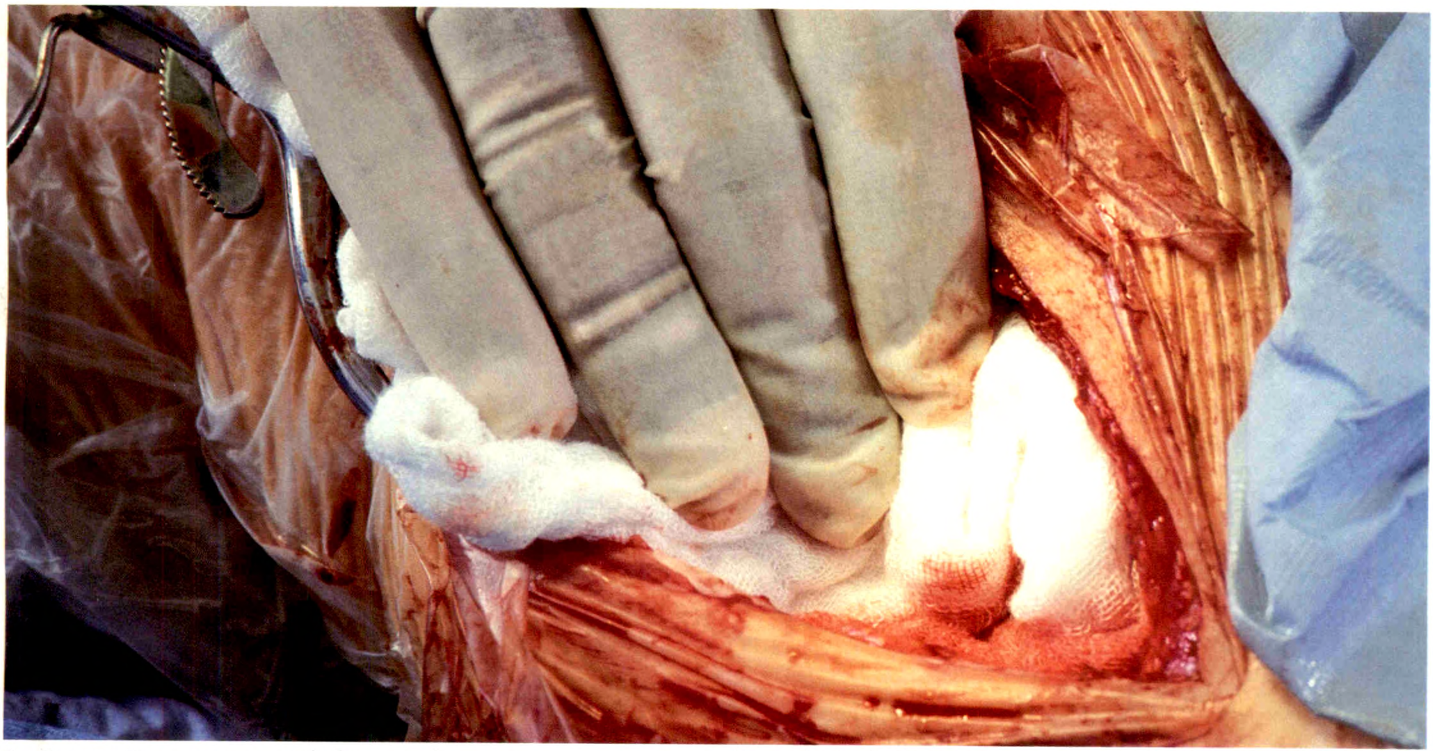
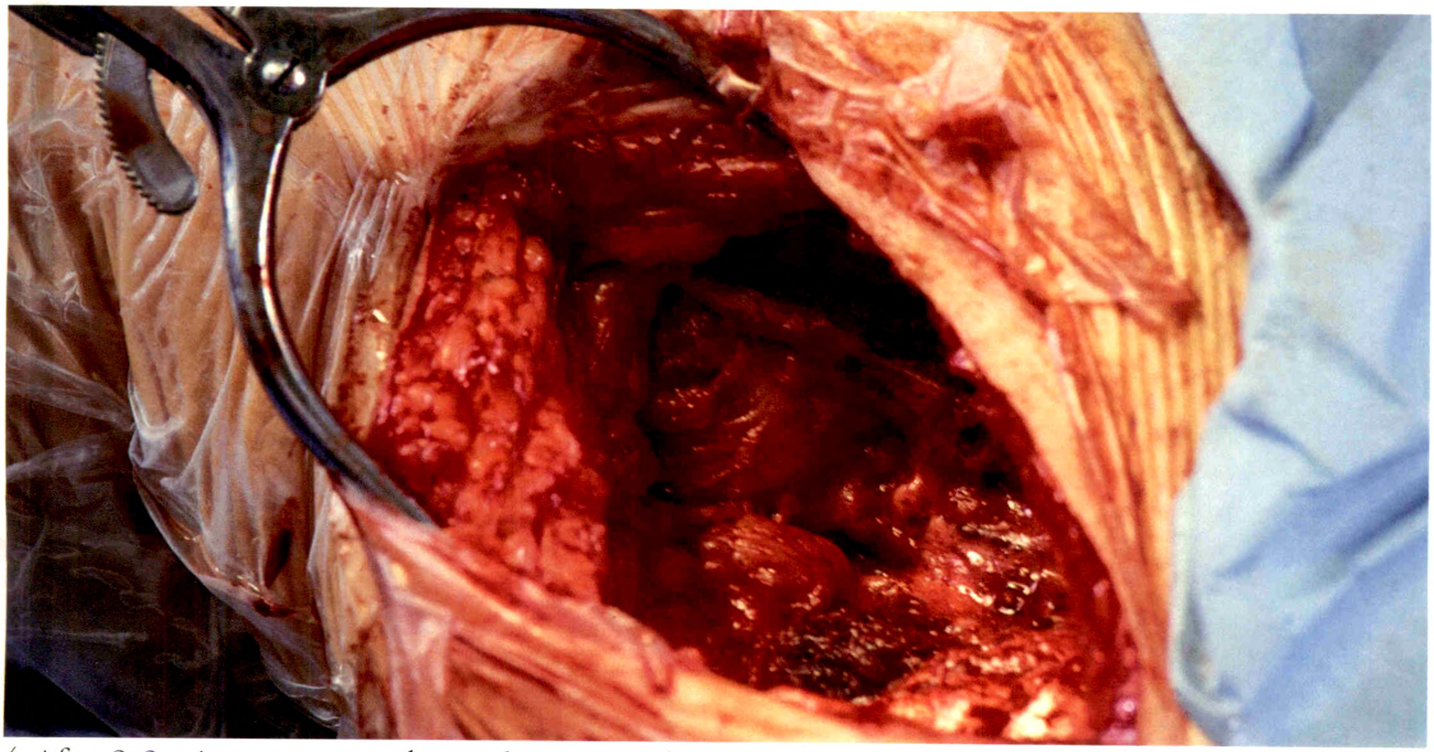


3. Cover Superstat with lap pad or gauze sponge and apply light pressure.



4. After 2-3 minutes, remove lap pad. Superstat has dissolved and hemostasis has occurred.

Superstat Modified Collagen Hemostat from Weck Surgical is a freeze-dried collagen sponge which has been treated to provide a net positive charge. In contact with shed blood, Superstat activates the coagulation mechanism and dissolves while carrying out its hemostatic effect.

It can be broken or cut into virtually any shape, and as it dissolves, it conforms to the bleeding site. Nonpyrogenic and nonantigenic, Superstat has shown no adverse effects on wound healing. Contact your O.R. supervisor so that you can evaluate Superstat in your next procedure.

Superstat®

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Superstat® is indicated for use when hemostasis is desired along suture lines in diffusely bleeding sites, incisions, dissections and around arterial or venous anastomoses. It is not intended to replace surgical ligature. Superstat® is indicated in oozing bleeding, either capillary or venous, in practically all incisions or wounds and as an adjunct to conventional closure techniques.

Contraindications

Superstat® is contraindicated in neurosurgical applications because no investigations on the effect of Superstat® on neurological tissue have been carried out to date. Superstat® is also contraindicated in instances of pumping arterial hemorrhage.

Directions For Use

The pad can be used in whole or in part to produce hemostasis at the point of bleeding. Superstat® should be applied dry to the bleeding site and covered with a sterile laparotomy pad or gauze sponge. The material will begin to soften as it is applied. Hemostasis should occur within two or three minutes after application. If hemostasis is not complete, a second application of Superstat® should be used. Superstat® will dissolve at the bleeding site. It is not necessary to remove excess materials. Residual clotted blood can be removed without causing further bleeding. Store Superstat® at controlled room temperature.

Precautions

In more profuse bleeding in which complete hemostasis is not observed, use of conventional surgical techniques may be necessary. Superstat® does not replace conventional surgical techniques such as clamping and/or ligation for severe bleeding. The use of Superstat® in patients with coagulopathies has not been fully evaluated. The effects of Superstat® used during pregnancy or its teratogenic potential have not been investigated.

Warning

Superstat® must be kept dry, moisture will cause Superstat® to lose its activity. Do not use Superstat® in instances of pumping arterial hemorrhage. Do not use Superstat® where blood or other fluids have pooled or in cases where the point of hemorrhage is submerged. Superstat® will not act as a tampon or permanent plug in a bleeding site nor will it close off an area of blood collecting behind a tampon. Discard unused portions of Superstat®. Do not resterilize Superstat®.

Superstat® Pledgets (above) and Discs (at left), shown at actual size, are both available in 1.5% and 3.0% concentrations.

Adverse Effects

Superstat® has shown no adverse effects on wound healing.

There are no known toxic effects.

The incidence rate of adhesion formation has not been investigated.

How Supplied:

Superstat® is a freeze-dried collagen sponge, supplied in 4″ x 4″ pledgets or 1¼″ discs, in double wrapped sterile trays. Five packages to a box in two concentrations: 1.5% and 3.0%.

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Sterility guaranteed if outer pouch is unopened and/or undamaged.

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The Expected Lifetime of Porcine Valves

Albert Starr, MD, and Gary L. Grunkemeier, PhD

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An important milestone has been reached with the availability of the 15-year results with porcine heart valves, including those of Magilligan and associates in this issue [1]. It is now possible to give a more complete characterization of the shape of tissue failure curves, and an adequate answer to the question, "What is the life of the valve?" It appears that for existing series the median lifetime has been reached at about 13 years. However, the information this is based on includes the first valve models and the earliest patients. Current selection of patients and further valve refinements may improve this durability record.

Magilligan and associates have produced an important contribution to the tissue valve literature. They report on over a thousand valves followed for up to 16.4 years with 99% completeness. Their definition of structural failure is conservative, requiring confirmation at explant.

This review will discuss the corroboration of their results in other reports, a mathematical description of the tissue failure curve, the concept of actual versus potential valve failures, and the implications of these findings in the context of alternative valve devices.

Figure 1 contains actuarial freedom from structural failure rates from the series of Magilligan and associates and six other series containing information beyond 10 years [2–7]. The 15-year points have large standard errors, ranging from 6% to 13%, but the points are fairly consistent, considering that different patients, valve models, positions, countries, and eras of implantation are involved. The failure pattern is also consistent with that for homograft valves beyond 10 years [8–11].

When the risk of an event is constant over time, the event-free curve has an exponential shape. The Weibull distribution is a generalization of the exponential distribution that accommodates a changing risk and is widely used in reliability studies. The median failure time for the Weibull curve in Figure 1 is 13 years. Unlike the median, calculation of the mean time to failure (average or expected lifetime) has to wait until every valve has failed. However, the Weibull model provides an estimate of the mean, which is also 13 years. The model also allows extrapolation beyond observed time, to 20 years in Figure 1, although such extrapolation must be interpreted cautiously.

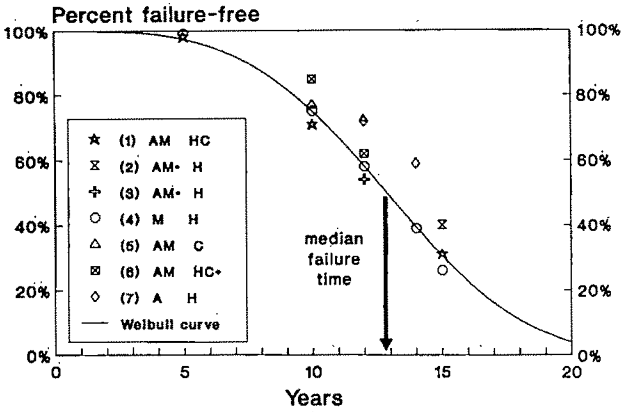

Fig 1. Failure-free percentages from published series with experience beyond 10 years, with Weibull curve fit to the points 75% at 10 years and 30% at 15 years (see text). This figure combines the aortic and mitral positions: three studies (AM) gave combined results, and for two (AM) we computed a weighted average. Valves used were Medtronic Hancock (H), Carpentier-Edwards (C), or both (HC), except for one series (HC+) that contained other porcine models as well as a small percentage of pericardial valves. The median failure time is the point on the horizontal axis directly below the intersection of the curve with the 50 percentile line.*

The model can further provide information about the effect of deaths on the percentage of valves that actually fail, as opposed to those potentially destined to do so. In computing failure-free curves, deaths are censored (withdrawn from the calculations in subsequent intervals) to get failure percentages based on only patients at risk. This provides an estimate of the underlying, potential risk of failure, called the net risk in the theory of competing risks (patient death and structural failure are competing for the valve). This *potential* rate measures the percentage of valves that would fail if no one died, or the risk of an individual being event-free if he or she is still alive. This is appropriate for comparing valves, because it does not depend on the death rate in the patient population, which can vary from one valve series to another. But the percent of *actual* failures is lower, as death precludes subsequent failure in patients who die before failure of their valve.

Figure 2 demonstrates that the potential failure-free rate of 30% at 15 years increases to an actual failure-free rate of 60% when the death rate for a typical valve series is taken into account. For a more elderly population, with a higher death rate, the actual failure-free percentage would be even higher.

The authors whose results are represented in Figure 1 drew opposite conclusions, some positive and some negative, regarding the acceptability of the porcine valve. This parallels the attitudes of the medical community, where both positions have advocates, though the risk of structural failure caused a reduction in the use of tissue valves in favor of mechanical valves beginning in the late 1970s. Using the concept of *treatment failure*, defined as valve-related death or permanent disability, tissue and mechanical valves were found to be comparable at 10

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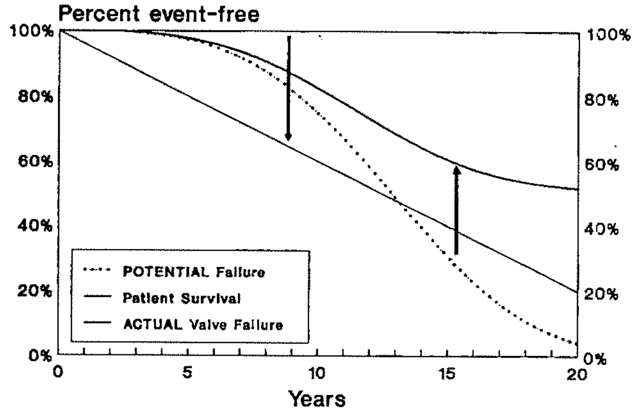

Fig 2. The dotted curve *is the* potential *Weibull failure-free curve from Figure 1. The* thin solid line *is the survival curve for a typical valve series, with 15-year survival of 40% (the 15-year survival rates for the series in Figure 1 ranged from 30% to 52%). The* thick solid curve *is the* actual *failure-free curve, which represents failures actually observed in the presence of the competing risk of death. The* upward arrow *indicates that the* potential *failure-free rates (30% at 15 years) increase to the* actual *failure-free rates (60% at 15 years) when deaths are taken into account, indicated by the* downward arrow *from the upper horizontal axis (= 100% survival) to the actual survival curve. If the patients had a lower survival rate, such as in a very elderly population, the actual valve failure-free curve would be higher.*

years [12]. This agrees with most comparison studies of tissue versus mechanical valves, including randomized clinical trials, which found an approximate balance of overall risks by 10 years [13].

Because a treatment failure comparison of mechanical and tissue valves at 15 or 20 years is not yet available, it is tempting to use the above model to speculate about such a comparison. According to the actual failure-free curve in Figure 2, 31 of every 100 implanted valves would fail between 10 and 20 years, which, if operated with a 10% mortality, would yield 3 deaths. This is roughly comparable with the actual number of deaths that would be expected to occur in a typical mechanical valve series from thrombotic (thromboembolism, thrombosis) and anticoagulant-related complications, in excess of tissue valves, based on weighted averages (0.6% to 0.8%/year) from Edmunds' literature review [14]. Thus we might speculate that the treatment failure equivalence at 10 years would be maintained during the second decade. However, this comparison is only approximate, because it assumes that all tissue failures come to operation and none lead directly to death, does not consider death from re-reoperation, and does not include nonfatal strokes. Also, treatment failure comparisons do not consider the costs of successful reoperations, to the patient in terms of suffering and to society in terms of expenses and resource utilization.

The porcine valve still appears to provide an acceptable alternative for many patients, and may improve in this regard. It is known that youth is a risk factor for structural failure, and recent evidence suggests that old age may be protective [2, 5, 15]. The mean age for five of the series in Figure 1 was 50 years or younger; thus there may be a further advantage in older patients due to their lower potential rate of valve failure. Improvement in tissue valve results may also come from changes to the valves themselves, such as the expected advantages of low pressure fixation and mitigation of calcification.

The fact that mechanical valves are available for patients who are poor risks for tissue valves may further enhance the clinical results achieved by the porcine valve [16]. In a complementary way, improved mechanical valve results will be achieved by better selection of patients according to the quality of future anticoagulation management. All of this underscores the need for an eclectic approach in selecting both types of prostheses for use according to patient-related variables such as age, lifestyle, and the risk of anticoagulation.

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Surgical Recanalization for Treatment of Evolving Myocardial Infarction

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In this issue Cheung and colleagues [1] present interesting results that lead them to suggest that surgical reperfusion may be warranted for treatment of acute myocardial infarction. In their study of experimental animals, they characterized myocardial mechanics and infarct size in dogs subjected to left anterior descending coronary artery occlusion. In 7 open-chest dogs, the vessel was simply ligated. In 8, reperfusion was induced by release of the occluding ligature after two hours. In 7, total cardiopulmonary bypass was instituted after two hours of occlusion with concomitant ventricular venting and intermittent cardioplegia with a basic, hyperosmolar perfusate that included red blood cells to enhance oxygenation, glucose and amino acids as substrate, allopurinol to inhibit oxygen-centered free radical formation from hypoxanthine, and citrate-phosphate-dextrose to decrease the concentration of ionized calcium. In this group, referred to as the *surgical reperfusion* group, reflow was initiated gradually and initially at low pressure. Dogs in the surgical reperfusion group manifested early improvement of systolic shortening measured with implanted sonomicrometers and by analysis of pressure–length relationships. Improved function was maintained and still evident 1 week later. Infarct size as a percentage of area at risk was lower than that in dogs subjected to either persistent occlusion or reperfusion without cardioplegia and without cardiopulmonary bypass. One week after occlusion, dogs subjected to reperfusion alone fared no better than those with persistent occlusion.

Although these results are intriguing, they do not, by themselves, justify proceeding to immediate cardiopulmonary bypass and cardioplegia as primary treatment of acute myocardial infarction. Several considerations may modify their interpretation.

Reperfusion "Injury"

The notion that reperfusion induces injury is somewhat ambiguous. Although reperfusion alone does not salvage myocardium to the maximum extent possible, it unequivocally attenuates evolution of infarction. Hemorrhage in reperfused myocardium is confined virtually exclusively to the ischemic region at risk. Morbidity and mortality associated with acute myocardial infarction are influenced favorably by reperfusion induced with thrombolytic agents [2, 3]. In recent large multicenter trials, mortality was reduced to 5% or less in patients treated with thrombolytic agents early after the onset of infarction as compared with an overall mortality of 8% to 12% among patients managed without thrombolytic agents. Thus, reperfusion is beneficial. Its limitations may reflect injury that is refractory to reperfusion or injury induced by reperfusion, but their sum is less than the countervailing benefit evident as a net, positive effect.

Factors Influencing the Fate of Reperfused Myocardium

The duration, severity, and distribution of antecedent ischemia before reperfusion are primary determinants of the extent of salvage that can be anticipated. Reperfusion within one hour after the onset of occlusion is associated with reduction in mortality and striking recovery of ventricular function [2, 3]. Results of laboratory and clinical studies have demonstrated some benefit when reperfusion is induced within intervals as long as six hours after the onset of ischemia [2–4]. However, the amount of myocardium that can be salvaged is inversely proportional to the duration of ischemia. In patients, collateralization may afford some protection to ischemic tissue and thereby delay the evolution of irreversible injury, widening the temporal window available for effective reperfusion to some extent. Furthermore, even though reperfusion more than four to six hours after the onset of ischemia may not salvage substantial amounts of myocardium, late reperfusion may decrease aneurysm formation or the incidence of malignant arrhythmia long after infarction.

Results of clinical studies indicate relatively little benefit when reperfusion is confined to the zone of supply of the right coronary system (patients with inferior infarction) compared with the benefit obtained when the left anterior descending or left circumflex coronary arteries are recanalized [2, 3]. The disparity probably reflects the relative amount of myocardium at risk in the two circumstances and the impact of the jeopardized zone on overall pump function of the heart. Clearly, patients with larger infarcts are more likely to sustain severe ventricular dysfunction and hence more likely to show benefit with revascularization than those with a small infarct that does not markedly impair overall cardiac function.

The adequacy of reperfusion is another key determinant of efficacy. In studies of experimental animals with induced thrombotic coronary occlusion, myocardial perfusion assessed with radiolabeled microspheres recovered immediately to 80% to 90% of normal when reperfusion was induced with either streptokinase or tissue-type plasminogen activator [5, 6]. However, 24 hours after recanalization with sustained patency of the coronary

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artery documented angiographically, blood flow to the reperfused region had diminished to only 50% to 60% of normal, presumably because of cell swelling, platelet plugging, or microvascular injury mediated by neutrophils. With time, myocardial blood flow subsequently increased again, albeit modestly [6].

Reperfusion through a persistently stenotic vessel in dogs results in failure of resolution of subendocardial ischemia and attenuation of diminution of infarct size [7]. Some clinical studies have reported enhanced benefit with a strategy of angioplasty combined with pharmacological thrombolysis despite the lack of demonstrable additional benefit of emergency as compared with elective angioplasty in large-scale multicenter trials [2, 3].

In the study reported by Cheung and colleagues, myocardial blood flow in ischemic zones was not different before reperfusion in the two treated groups. However, flow measurements were not repeated early after the onset of reperfusion. The differences in ventricular function and in infarct size observed may reflect a disparity in the adequacy of early reflow. In dogs in the surgical reperfusion group, nutritive reflow may have been greater because cardioplegic solution relatively or absolutely devoid of platelets and white blood cells was used. The low pressure may have minimized tissue edema. These factors coupled with the benefits of ventricular venting may have facilitated more complete reperfusion and the salutary results observed [8].

Influence of Adjunctive Agents

Although Cheung and colleagues conclude that the intrinsic nature of surgical reperfusion accounted for the benefits observed, other factors may have been responsible. Concomitant treatment with calcium-channel inhibitors or oxygen free radical scavengers can enhance salvage induced by reperfusion. In a study from our laboratory, administration of diltiazem beginning before reperfusion at a dose that did not alter ventricular afterload, heart rate, or myocardial blood flow decreased infarct size by 50% compared with the reduction induced by reperfusion alone [5]. This augmentation of salvage is strikingly similar to that observed in the dogs studied by Cheung and colleagues in the surgical reperfusion group. The decreased calcium content of the cardioplegic solution used may have contributed.

The role of oxygen-centered free radicals in reperfusion injury is less clear. Although some investigators have reported that scavengers of these agents enhance salvage induced by reperfusion, results have been inconsistent. In the study by Cheung and associates, allopurinol in the cardioplegic solution may have been beneficial in scavenging oxygen-centered free radicals formed from hypoxanthine through the xanthine oxidase pathway. The role of this biochemical pathway in human subjects is probably minimal, however, because human myocardium does not exhibit readily detectable xanthine oxidase/xanthine dehydrogenase activity.

The cardioplegic solution used in the Cheung study contained glucose, glutamate, and aspartate, and had a high pH. Several substrates enhance salvage compared with that induced by reperfusion alone, perhaps because functional recovery of reperfused myocardium appears to depend on prompt restoration of oxidative metabolism.

The ventricular unloading used in the Cheung study for the surgical reperfusion group may have contributed to the benefit apparent in the surgical reperfusion group [9]. Decreased myocardial afterload, which favorably affects the oxygen supply/demand ratio, enhances salvage. In the recently reported TIMI II study [10], β blockade reduced the incidence of recurrent ischemia after thrombolysis induced with tissue-type plasminogen activator. In animals, decreased ventricular work induced by nonsurgical approaches favorably alters recovery of reperfused myocardium. The local and whole-body hypothermia used in the surgical reperfusion group in the Cheung study would contribute to reduction of myocardial oxygen requirements as well and may enhance recovery per se [11].

Is Surgical Reperfusion Warranted for Patients With Acute Myocardial Infarction?

From the experimental design used by Cheung and colleagues it is not possible to determine which components of the protocol were responsible for the favorable results in the surgical reperfusion group. Serious logistic difficulties preclude routine use of cardiac surgery for patients with acute myocardial infarction. Most such patients are seen initially in community hospitals that lack facilities and staff necessary for immediate assessment of coronary arterial anatomy angiographically. The time required to acquire such information before operation would probably preclude salvage of the magnitude observed in the Cheung study, in which aortic cross-clamping could be initiated after only two hours of ischemia. Because other adjunctive measures such as calcium channel blockade, diminution of ventricular afterload, administration of oxygen-centered free radical scavengers, and provision of alternative myocardial substrates may be as effective with pharmacological thrombolysis as they may have been in the surgical reperfusion group in the study of Cheung and colleagues, these and other approaches merit evaluation in patients as adjuncts to pharmacological thrombolysis [12]. In the small number of patients with evolving myocardial infarction in whom thrombolysis is unsuccessful or in those in whom myocardial ischemia is refractory to medical management, emergency operation may be required and is remarkably safe [13]. However, despite the intriguing results obtained by Cheung and colleagues, most patients with acute myocardial infarction are likely to continue to be managed medically.

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A more complete bibliography is available from the authors.

Evolving Techniques in the Management of Benign Esophageal Stricture

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The treatment of esophageal strictures associated with primary or secondary reflux disease remains a challenge for the esophageal surgeon. The philosophy of treatment varies so much between institutions that no uniform attitude is agreed upon between gastroenterologists, and even among surgeons themselves.

The paper in this issue by Ramirez Schon and associates [1] is a confirmation of this situation in that they propose to use a gastric vascular pedicle patch esophagoplasty to correct esophageal strictures. As proposed, this operation is a variation of the Hugh patch repair. Arguing that antral mucosa is acid-resistant and has the added advantage of not secreting acid, Hugh and co-workers [2] experimented with this method in dogs, showing that it had no deleterious effects on the esophagus. They also argued that patches derived from the more proximal stomach body are likely to secrete acid and pepsin, thereby exposing the adjacent esophagus to ulceration. Hugh and associates [3] applied their observations in 15 patients, creating an antral patch based on the left gastroepiploic artery. Their results, updated in a recent textbook [4], showed this operation to be safe and effective in correcting dense esophageal strictures. Of the 15 patients, 4 had reflux strictures with scleroderma, 1 had a stricture after esophageal trauma, 2 had a reflux stricture from a previous myotomy for achalasia, and 8 had intractable strictures from gastroesophageal reflux disease after an unsuccessful antireflux operation. In their follow-up, which ranged from 6 months to 9 years, Hugh reports that 3 patients still require occasional dilations and that evidence of esophagitis proximal to the patch has occurred in 4 patients.

From these reports, there is no doubt that a stricturoplasty is feasible using a well-vascularized gastric patch of either antrum or fundus. A patch of jejunum or colon would achieve the same purpose, for that matter. It is another problem, however, to correct the reflux that led to this stricture and maintain adequate esophageal lumen permeability. A narrowed and shortened esophagus rarely allows a proper tension-free fundoplication under the diaphragm (and under the patch). The report by Ramirez Schon and associates does not offer a nonsubjective follow-up, except for the 1 patient in whom the esophagus was removed for a diagnosis of esophageal carcinoma and the cancer was not found after the esophagectomy. It is worrisome to see an operation used without more evidence of its success than the technical success of the operation itself. Neither the initial reports by Hugh and associates nor the report by Ramirez Schon and co-workers offer any proof that the underlying reflux problems have been corrected. Moreover, the need for long-term dilations and the presence of esophagitis proximal to the patch in 7 of 15 patients reported by Hugh and associates underlines the need for long-term objective follow-up with the aid of endoscopy, biopsies, pH studies, and motor function evaluation.

Standard antireflux operations fail in a larger proportion of cases when a stricture is present than if there is less damage. Variations in attitudes and new surgical techniques stem from this simple observation. The esophagus, strictured from long-term reflux or damaged with extensive columnar epithelium replacement, is frequently affected by periesophagitis and shortening. Even after extensive esophageal mobilization to the aortic arch and freeing of the esophagogastric junction, an easy reduction of an appropriate 4 to 5 cm of esophagus under the diaphragm may be difficult, and a tension-free repair may not be possible. For these reasons Thal [5] proposed to split the strictures and widen the esophagus by a fundic serosal patch. Later a skin graft had to be added to avoid restricturing. However, even if the stomach serosa was protected, this repair suffered from free reflux and recurrent esophagitis. Total fundoplication added to the patch gives satisfactory long-term results in 84% of patients [6]. A simple total fundoplication without stricture splitting and left in the chest was also reported in the mid 1960s by Krupp and Rosetti [7]. Recently reviewed by Maher [8], this operation was shown to offer good to excellent results in 82% of patients. Both types of intrathoracic fundoplications, although known to correct the reflux problem, are not used extensively because of the dangers reported with supradiaphragmatic fundoplications: paragastric diaphragmatic hernias, gastric ulcerations, and gastric fistulization with mediastinal structures.

Esophageal sparing procedures besides intrathoracic fundoplications are the lengthening operations proposed by Collis [9] and subsequently modified to include a partial fundoplication [10] or a total fundoplication [11]. When assessed with pH studies, reflux control is confirmed in 75% of the operated population, whereas the other 25% (despite subjective satisfaction) still show active reflux episodes.

Is there a place for a gastric patch operation in the management of benign esophageal strictures? Reflux disease must be looked at with a long-term perspective where one needs to be careful not to "burn bridges" too early. The stomach is one of those bridges, as it may be used eventually as an appropriate replacement organ if the esophagus is to be removed later. It is presently

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emerging as a very satisfactory alternative to colon or small bowel interposition after resection for benign conditions. The patch operation, although it may offer satisfactory opening of the esophageal lumen, actually requires the sacrifice of an organ that may be subsequently needed to replace an esophagus damaged by the chronic complications of reflux disease. The natural evolution of the columnar-lined esophagus should be an added warning that even if the reflux is controlled, malignant transformation may still occur and require subsequent resection and reconstruction.

For these reasons we believe that the role of vascularized gastric patches should be restricted to those patients in whom intractable strictures require an esophageal salvage procedure, and a resection of the gastric antrum is indicated to accompany a Roux-en-Y pancreatobiliary diversion. Even in these situations the patch operation should then be gauged against the results of esophageal stricture resection and esophagogastrostomy coupled with duodenal diversion by the Roux-en-Y technique, as reported by Payne [12].

When possible, dilation and simple fundoplication remains the most effective procedure to protect the esophagus against reflux damage. If an appropriate tension-free reduction of the distal 4 to 5 cm of the esophagus under the diaphragm cannot be obtained, a lengthening procedure gastroplasty accompanied by total fundoplication around the gastroplasty gives the advantage of reflux control while protecting an adequate stomach length for eventual use if the esophagus is later resected.

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The Porcine Bioprosthetic Heart Valve: Experience at 15 Years

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The porcine bioprosthetic valve has been in use at Henry Ford Hospital since 1971. In this review, 980 patients with 1,081 porcine bioprosthetic valves were examined from 1 month to 16.4 years after implantation with a 99% complete follow-up. Patient survival was 59% ± 2.2% (± standard error of the mean) at 10 years and 38% ± 4.0% at 15 years. Factors associated with decreased survival after hospital discharge were age greater than 35 years and New York Heart Association functional class IV. Freedom from thromboembolism was 92% ± 1.2% at 10 years and 89% ± 3.2% at 15 years. Freedom from endocarditis was 93% ± 1.2% at 10 years and 92% ± 1.3% at 15 years. Freedom from structural valve degeneration for all valves was 71% ± 2.6% at 10 years and 31% ± 5.6% at 15 years. Factors associated with increased risk of structural valve degeneration were age younger than 35 years, female sex, and preoperative cardiac index greater than 2 L/min/m^2. Among a total of 172 patients undergoing removal of a degenerated valve, mortality was 12.5%, and significant risk factors for death at reoperation were emergency operation and functional class IV. Experience with the porcine bioprosthetic valve after 15 years suggests that its use be confined to older patients or patients with a contraindication of anticoagulation.

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The commercially prepared porcine bioprosthetic heart valve has been available for clinical use since 1970 and used at Henry Ford Hospital since 1971. Its early performance, assessed at 5 years, revealed a low thromboembolism rate and an incidence of structural valve degeneration of less than 5% [1–3]. Intermediate-term results showed that at 10 years, the rate of thromboembolism remained low, structural valve degeneration was excessive in young patients, and for patients older than 35 years, there was an incidence of structural valve degeneration of 20% [4]. The prediction of Carpentier [5], the originator of the glutaraldehyde-fixation process, that valve failure would be 20% at 10 years was unfailingly accurate. Now the cumulative experience with the porcine bioprosthetic valve has matured, and late results of the performance of the prosthesis are available at 15 years.

Material and Methods

The porcine bioprosthetic valve has been used in Henry Ford Hospital since October 1971. Between that time and December 1987, there were 980 patients who were hospital survivors of an operation at which a first porcine valve was implanted. For purposes of analyzing patient survival and the risk factors associated with valve-related events, only this group was examined to eliminate the effect of a second porcine valve implanted at a later time or of multiple prostheses of different types. Among these 980 patients, a total of 1,081 valves were placed: 492 aortic, 554 mitral, and 35 tricuspid. Seventy-two percent were Hancock and 28%, Carpentier-Edwards valves.

Age of the patients ranged from 6 to 87 years (mean age, 55.2 ± 14.8 years (± standard deviation). There were 532 male and 448 female patients. Follow-up ranged from 1 month to 16.4 years, and the mean follow-up was 5.8 ± 3.7 years. Total follow-up was 5,650 patient-years. During the year 1987, all but 11 of the 980 patients were accounted for, thus making follow-up 99% complete.

Thromboembolism was defined as all new focal neurological deficits, either transient or permanent, or any noncardiac-related, sudden arterial occlusion. Endocarditis was defined as one or more of the following: two positive blood cultures; an infected embolus examined histologically or bacteriologically; or histological and bacteriological examination of an explanted valve. Structural valve degeneration was defined as valvular incompetence or stenosis with degenerative changes confirmed on gross and histological examination of the explanted valve and without any bacteriological or histological evidence of infection.

Patient survival included operative mortality and was calculated by the life-table survival method [6]. Freedom from thromboembolism, endocarditis, and structural valve degeneration was calculated by the life-table method [6], and confidence limits were calculated by Greenwood's formula [7]. Because valve-related events did not occur at a constant rate, the hazard function was calculated in yearly intervals [8]. Individual aortic and mitral valve freedom from structural degeneration was examined independent of the patient, as recommended by Bodnar and associates [9]. Comparison between

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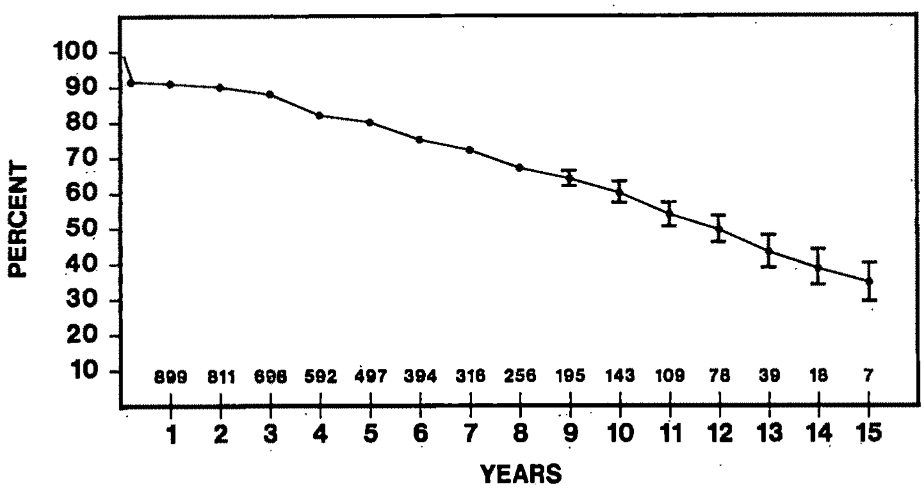

Fig 1. Patient survival (all porcine valves) was 80% at 5 years, 59% at 10 years, and 38% at 15 years.

groups was determined by the log-rank statistic [10]. Multivariate risk analysis for valve-related events was performed by the Cox proportional hazards regression model [11]. Stepwise logistic regression was used to perform the risk-factor analysis for death after hospital discharge following initial porcine valve implantation and after reoperation.

Risk factors examined for late death, thromboembolism, endocarditis, and structural valve degeneration were as follows: age, sex, New York Heart Association class, presence of coronary artery disease, previous myocardial infarction, rhythm, valve position, valve type (Hancock or Carpentier-Edwards), presence of anticoagulation, preoperative mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac index less than 2 L/min/m^2 or 2 L/min/m^2 or greater. For risk of death at reoperation, to these risk factors were added the following: the number of the open heart procedure, operative procedure, and status at operation, ie, emergency (operation necessary within 24 hours of catheterization or admission because of symptoms), urgent (operation necessary within six days of catheterization or admission because of symptoms) and elective (operation performed seven or more days after catheterization or admission or if earlier, operation not dictated by severe worsening of symptoms).

Results

Patient Survival

Patient survival with operative mortality included was 80% ± 1.4% (± standard error of the mean [SEM]) at 5 years, 59% ± 2.2% at 10 years, and 38% ± 4.0% at 15 years (Fig 1). Risk factors associated with late death after hospital discharge were age greater than 35 years ($p = 0.03$, relative risk = 1.5) and New York Heart Association class IV ($p = 0.0005$, relative risk = 1.8 versus class II and 1.1 versus class III).

Thromboembolism

Freedom from thromboembolism for all valves was 96% ± 0.7% (SEM) at 5 years, 92% ± 1.2% at 10 years, and 89% ± 3.2% at 15 years (Fig 2). The hazard function for thromboembolism showed a high early risk and a lower but continuous risk later (Fig 3).

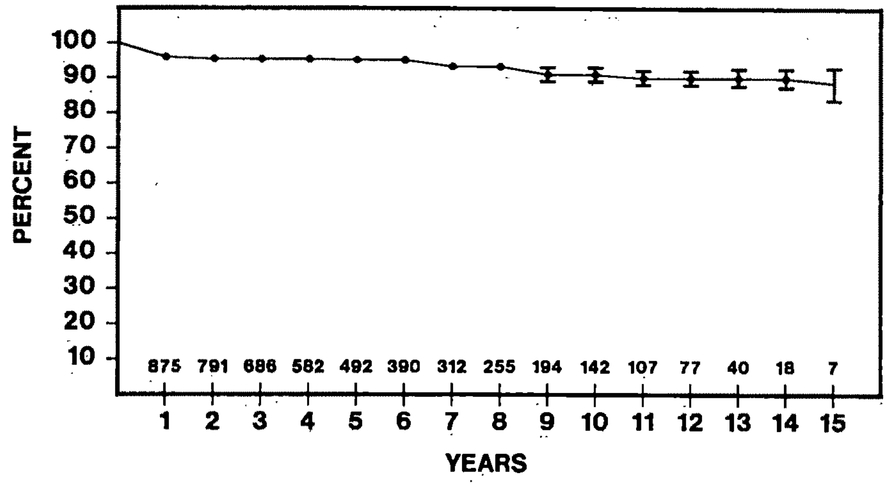

Fig 2. Freedom from thromboembolism (all porcine valves) was 92% at 10 years and 89% at 15 years.

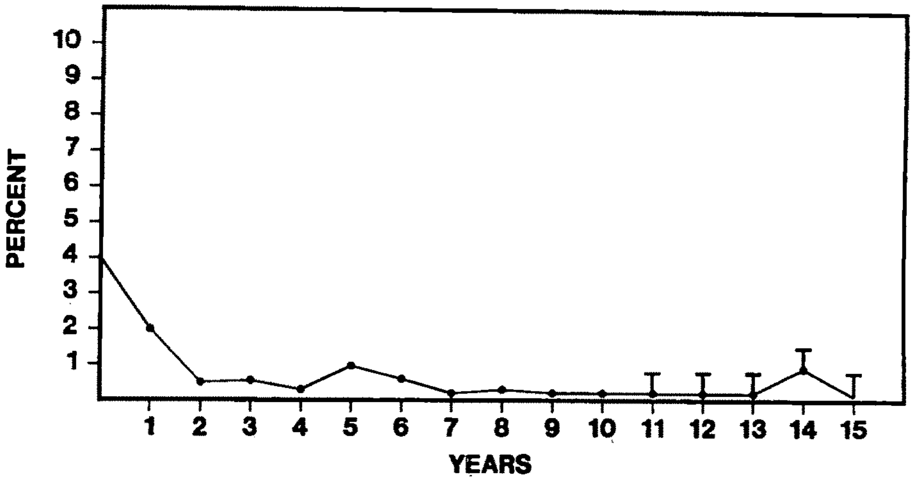

Fig 3. The hazard function for thromboembolism (all porcine valves) showed a high early risk and a lower but continuous risk later.

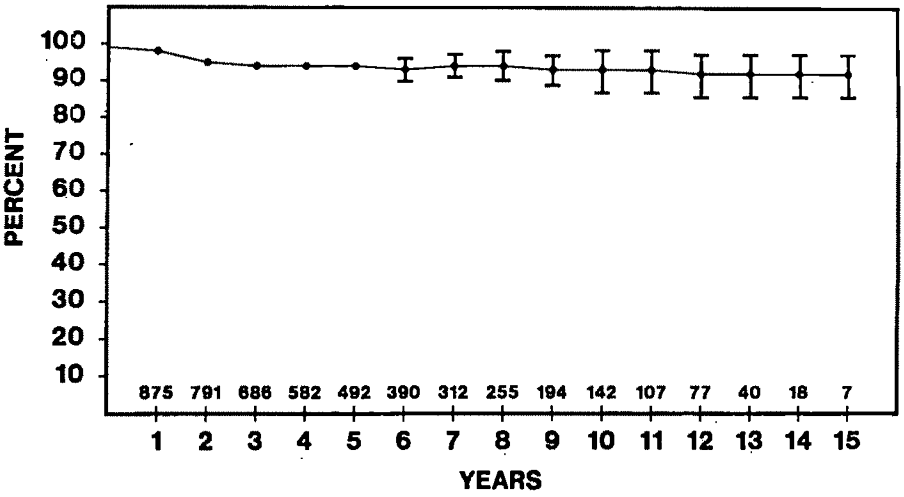

Fig 4. Freedom from endocarditis (all porcine valves) was 93% at 10 years and 92% at 15 years.

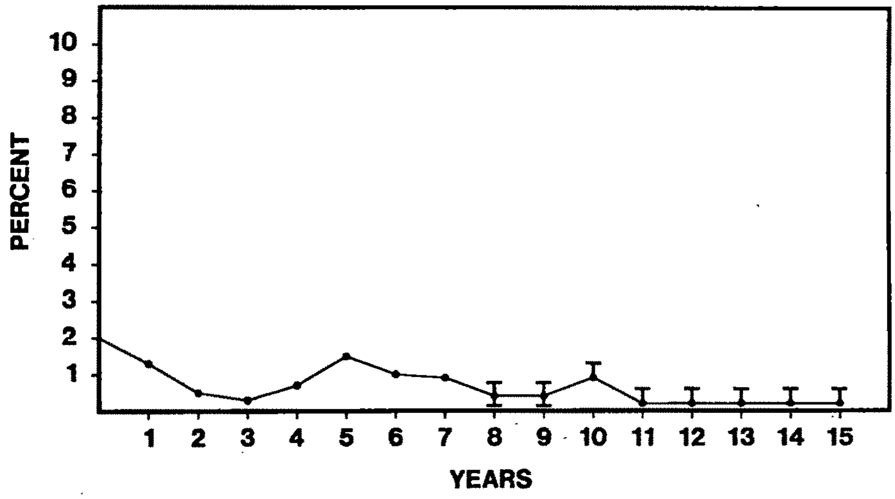

Fig 5. The hazard function for endocarditis (all porcine valves) showed a continuous, low risk of endocarditis.

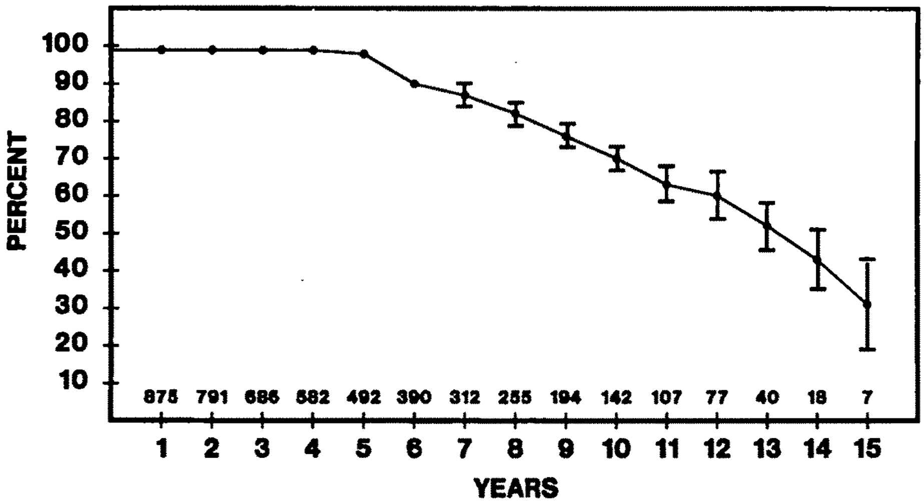

Fig 6. Freedom from structural valve degeneration (all porcine valves) was 71% at 10 years and 31% at 15 years.

Endocarditis

Prosthetic valve endocarditis has occurred 56 times. Patient characteristics and the risk of factors associated with prosthetic valve endocarditis have been extensively reported [12]. Freedom from prosthetic valve endocarditis was 96% ± 0.7% (SEM) at 5 years, 93% ± 1.2% at 10 years, and 92% ± 1.3% at 15 years (Fig 4). The hazard function showed a continuous, low risk of endocarditis (Fig 5).

Structural Valve Degeneration

The freedom from structural valve degeneration for 980 patients with a first porcine valve operation was 98% ± 0.6% (SEM) at 5 years, 71% ± 2.6% at 10 years, and 31% ± 5.6% at 15 years (Fig 6). Freedom from structural valve degeneration for all aortic valves was 98% ± 0.8% (SEM) at 5 years, 76% ± 4.2% at 10 years, and 37% ± 11.2% at 15 years (Fig 7). For all mitral valves, freedom from structural valve degeneration was 97% ± 0.9% (SEM) at 5 years, 71% ± 3.1% at 10 years, and 30% ± 6.5% at 15 years (Fig 8). The hazard function showed a steady rise in structural valve degeneration from years 6 through 10 and a marked rise after year 11 (Fig 9).

Significant factors associated with structural valve degeneration after the first porcine valve implantation were age less than 35 years ($p = 0.001$, relative risk = 1.5), female sex ($p = 0.05$, relative risk = 1.2 versus male sex), and cardiac index greater than 2 L/min/m^2 ($p = 0.04$, relative risk = 1.7 versus cardiac index less than 2 L/min/m^2).

Reoperation

Reoperation for porcine valve structural degeneration was carried out 165 times for a first valve failure. Mortality at 30 days was 13.3% (22 patients). An additional 11 patients had reoperation for a second valve failure with no deaths. Overall mortality for reoperation for structural valve degeneration was 12.5%. Stepwise logistic regression analysis was used to determine the risk of dying at reoperation for structural valve degeneration. Significant risk factors for death at reoperation were emergency operation ($p = 0.003$, relative risk = 4.1 versus elective operation and 1.3 versus urgent operation), and New York Heart Association class IV ($p = 0.005$, relative risk = 5.5 versus class III).

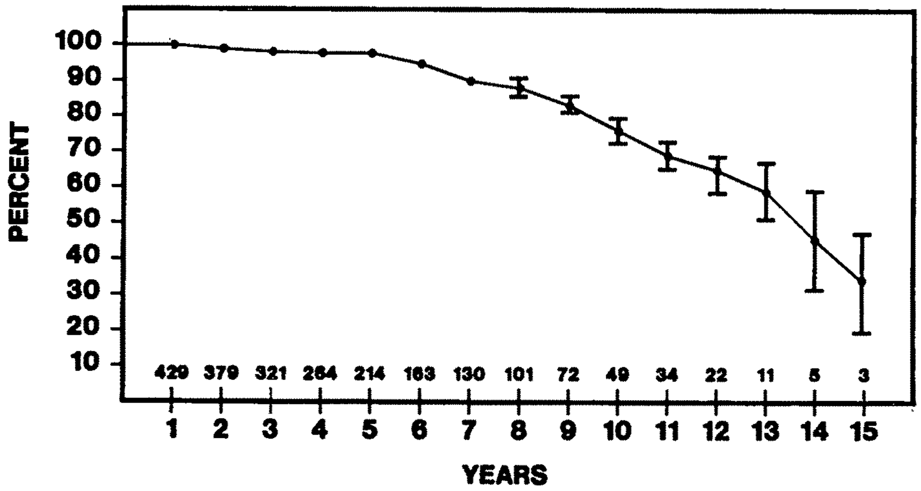

Fig 7. For aortic valves, freedom from structural valve degeneration was 76% at 10 years and 37% at 15 years.

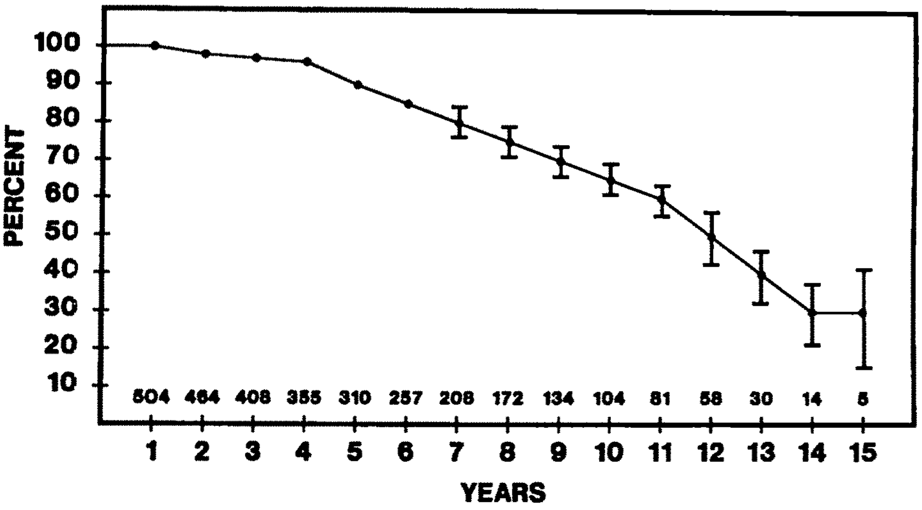

Fig 8. For mitral valves, freedom from structural valve degeneration was 71% at 10 years and 30% at 15 years.

Comment

The porcine bioprosthetic valve emerged on the scene a scant 9 years after the Starr-Edwards ball-valve prosthesis [13] and 1 year after the Björk-Shiley tilting-disc valve [14]. This glutaraldehyde-treated, stent-mounted porcine aortic valve can now rightfully be called an older heart valve prosthesis.

At its initial clinical use, the valve was heralded as an improvement over mechanical valves because of its low rate of thromboembolism and its freedom from anticoagulation-related hemorrhage. In addition, it was predicted to provide improvement over the initial experience with homografts [15] and fascia lata valves [16], as the glutaraldehyde process would make it more durable and more resistant to infection.

The rate of thromboembolism with the porcine bioprosthetic valve continues to be low at 15 years. Although others [17] have suggested that many embolic events occur in the first months after valve implantation, the hazard function for our data suggests that although the risk is highest initially, it is continuous (see Fig 3). Our knowledge of the true incidence of and the risk factors for thromboembolism are imprecise, as described by McGoon [18].

Our early experience showed that the porcine valve, unlike previous tissue valves, could be sterilized in the face of prosthetic valve endocarditis [19]. The early optimism, however, was soon limited by the fact that the number of deaths due to endocarditis of porcine valves was no different from that of mechanical valves [20]. Currently the number of deaths caused by prosthetic valve endocarditis is lower than a decade ago, most likely because of improved antibiotics. However, even though it has become easier to sterilize the porcine bioprosthesis, our group [21] has noted that a prosthetic valve successfully treated medically for endocarditis and without evidence of destruction will undergo structural valve degeneration sooner than other porcine valves.

Structural valve degeneration, unrelated to infection, remains the major deficiency of the porcine valve. The freedom from structural valve degeneration at 15 years of 31% is similar to the equivalent experience of other investigators [22–24]. As in previous studies, age less than 35 years is a significant risk factor. For the first time in our

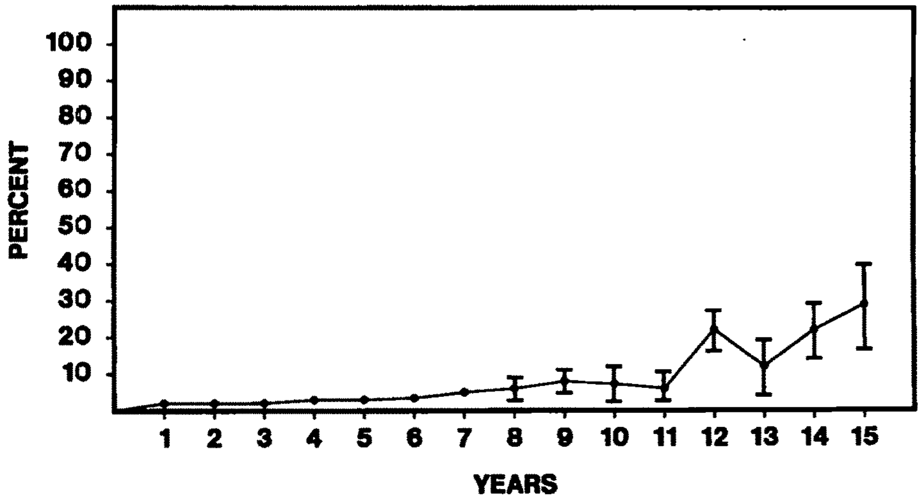

Fig 9. The hazard function for structural valve degeneration (all porcine valves) showed a steady rise from years 6 through 10 and a marked rise after year 11.

analysis, female sex appeared as a significant independent risk factor.

The fact that a cardiac index greater than 2 L/min/m^2 prior to porcine valve implantation appeared to be a significant risk factor for structural valve degeneration suggests a role for mechanical stress as a common cause of all tissue valve failure. We know that tissue valves fail at the site of greatest stress [25]. Calcification in the porcine valve also occurs at the site of the greatest mechanical stress [25, 26]. It is therefore most likely that calcification does not occur as a primary event, but that mechanical stresses damage the structural integrity of the valve and lead to valve failure with or without calcification. This would explain why failure occurs more frequently with young age, pregnancy, and renal failure, when heart rates are higher [27].

Reoperation for structural valve degeneration in a total of 176 instances resulted in a 12.5% mortality, which is similar to the long-term experience of others [28, 29]. In the Cox model, emergency operation and New York Heart Association class IV were associated with a significant risk of death at reoperation. It is clear that to decrease the incidence of death at reoperation, the incidence of emergency reoperation must be lowered by increased surveillance. An assessment of the hazard function for structural valve degeneration (see Fig 9) suggests that clinical and echocardiographic evaluation of valve function be performed annually in years 1 through 5, semiannually in years 6 through 10, and quarterly thereafter.

In the 15 years of use of the porcine bioprosthetic valve, the follow-up has been intensively investigated. The valve has fulfilled the expectations in regard to thromboembolism. Structural valve degeneration occurring at a rate of 30% at 10 years in both young and older patients and up to 70% at 15 years suggests that its use be confined to older patients or patients with a contraindication to anticoagulation.

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DISCUSSION

DR LAWRENCE H. COHN (Boston, MA): From 1970 to 1972, six institutions around the world began a clinical investigation of the use study that Dr Magilligan has presented. These institutions included the group at Padua, Italy, the Oklahoma City group with Dr Zuhdi, the National Institutes of Health, Brigham and Women's Hospital (then called Peter Bent Brigham Hospital), Stanford University, and Henry Ford Hospital.

These institutions have consistently prepared long-term reports such as the one we have just heard. I think these reports, like the report of Dr Magilligan, have given an excellent and honest evaluation of this valve, perhaps in greater detail than for any other valve that has ever been studied. From the analysis of these data, I think that the porcine valve is a very reasonable 10-year valve, ie, structural degeneration begins to increase significantly at about this point. Of course, the data analyzed, like Dr Magilligan's data, are taken from a large number of patients in different age groups and with a number of different risk factors. My colleagues and I know from our own work and from work by Dr Pupello in Florida that the probability of valve dysfunction is much less in the elderly age group at 10 years than in younger patients.

We looked at our data on 1,678 Hancock valves that we have implanted over the last 16 years at Brigham and Women's Hospital. Our data show similar findings to those of Dr Magilligan. In our personal group of 825 Hancock porcine aortic valve replacements, begun in 1972, structural valve degeneration correlates very nicely with the hazard risk, documenting an increase in dysfunction after about 10 years. At 12 years, the probability of freedom from structural valve degeneration was 72% ± 5% and at 14 years, it was 59% ± 8%, with a hazard of 17% ± 12%. I believe the new term *structural valve degeneration* is going to become more popular in view of the guidelines published in *The Annals* and *The Journal of Thoracic and Cardiovascular Surgery* in September.

Our data are roughly similar to those of Dr Magilligan, although slightly more optimistic. Again, any difference may represent the difference in demography, which has to be very carefully analyzed in any valve study. For example, the mean age in our group was 65 years, and we had no patient less than 21 years of age.

The other thing to remember is that at the end of the actuarial curves in this study, ie, at 15 years, the number of patients at risk is extremely small. Hence, any event that occurs in that end-study group makes a very sharp decline in the actuarial curve. I think it is important to present all the data, but on the other hand, it may not be possible to make a valid statistical conclusion at 15 years.

This may be a moot point, because with the number of reoperations and the age of patients with decreased survival and the number of patients with coronary artery disease, for example, we may never be able to get a big enough cohort with porcine valves. Dr Magilligan, I would appreciate your comments on the statistical validity of the 15-year points that you have mentioned.

Based on our work with a large number of porcine valves, we believe, as does Dr Magilligan, that the time has come to redefine the indications for use of porcine bioprosthetic valves. It is an excellent valve for the elderly patient, defined as older than 65 years. It is an excellent valve when there are contraindications to anticoagulation, when the patient is a female patient of childbearing age or one who wishes to have children, and when any patient has a particular preference for a biological valve.

Finally, I congratulate Dr Magilligan for the persistence, industry, and effort necessary to do this kind of analysis for 15 consecutive years.

DR ROBERT W. M. FRATER (Bronx, NY): There are two questions I have for Dr Magilligan. I was intrigued by the cardiac index of more than 2 as a factor in valve deterioration, and I agree with the premise that physical stress is probably important in this. However, I wonder if it is possible that all the patients with a cardiac index of less than 2 did not live long enough for valve degeneration to develop, because that is an extraordinarily low index and surely was a negative prognostic factor for patient survival.

The other question is whether it is reasonable to draw a conclusion about use of this valve based on this experience. Surely we would need to look at the experience with all valves to decide which valve to use in a given circumstance. If you decide not to use this valve under certain circumstances, you must have an alternative in mind. Should we not be looking at patient survival that is relatively complication free with different devices to decide which device is appropriate for which patient, rather than determining that we will not use the Hancock valve under certain circumstances because of its isolated performance?

DR WATTS R. WEBB (New Orleans, LA): I notice that you have used these valves in children as young as 6 years. In view of your experience now and the danger of calcification in the growing child, what age would you recommend as the minimum for putting this valve in children?

DR MAGILLIGAN: Thank you. Dr Webb, we would not put a porcine bioprosthetic valve in a child. We would perform reconstructive procedures to a great extent, even leaving some valvular insufficiency, use a mechanical prosthesis, or possibly use a homograft in the aortic position.

We appreciate Dr Cohn's comments. I think the conclusions of everyone are the same; that failure increases dramatically after 10 years and that the valve has a reasonably acceptable life span up to 10 years.

Dr Cohn questions whether we should report the leading edge of the actuarial curve. It is true that beyond 15 years, there were only 7 patients to be analyzed. In any event, these patients would markedly decrease the curve as demonstrated by the associated SEM or confidence limits. I think it is important that we present the curve and leave the interpretation to the reader. However, the readers have to look at all the data presented with some degree of intelligence. I think that not reporting such data is a greater failure than reporting them.

Dr Frater, I think that we do need to look at all valve prostheses, and in practicing cardiac surgery, I think that is what we all do. We make a choice based on information available. We did not talk about other valves simply because I do not have the same kind of information about other valve prostheses.

Reperfusion of Infarcting Myocardium: Benefit of Surgical Reperfusion in a Chronic Model

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Surgical reperfusion of experimental infarction leads to improved recovery of regional function compared with medical reperfusion, but sustained myocardial salvage has not been demonstrated. Twenty-two dogs were subjected to two hours of anterior descending occlusion and divided into three groups: group P ($n = 7$), no reperfusion; group M ($n = 8$), medical reperfusion; and group S ($n = 7$), controlled surgical reperfusion. Ischemia caused systolic bulging (−36% of control systolic shortening, $p < 0.01$) and decreased regional work (9% of control pressure-length loop area, $p < 0.05$). Thirty minutes after reperfusion group M had persistent systolic bulging (−9% of control systolic shortening) and decreased regional work (9% of control pressure-length loop area), whereas group S had +17% of control systolic shortening and 33% of control pressure-length loop area. After 1 week, regional function improved in all three groups (percent of control systolic shortening: group P, 26%; group M, 19%; group S, 52%), but systolic shortening was significantly better in group S ($p < 0.05$ versus group M). Surgical reperfusion also resulted in one half of the eventual myocardial necrosis found in the other groups (group P, 45% of area at risk; group M, 38%; group S, 19%; $p < 0.05$, group S versus group P or M). In this model, medical reperfusion offered no demonstrable benefit, whereas controlled surgical reperfusion led to a sustained (1 week) improvement in regional function and significant myocardial salvage.

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Early reperfusion of acute myocardial infarction has become, with the advent of thrombolysis and angioplasty, the prerogative of the invasive cardiologist. Although such methods are successful in restoring coronary patency, investigations of experimental infarction have demonstrated that simple restoration of flow may produce additional injury [1, 2]. This reperfusion injury appears to be multifactorial in etiology, and may be minimized if the conditions of reperfusion and the reperfusate itself are modified [3–16].

Reperfusion that utilizes surgical techniques of cardiopulmonary bypass and cardioplegic arrest offers an unusual opportunity for control of reperfusion after regional ischemia. Several experimental studies have demonstrated an improvement in acute functional recovery and infarct size with the use of supplemented blood cardioplegic solution [3, 4, 9, 10, 12, 15]. Results in these studies were recorded within a few hours after infusion of a modified reperfusate had been completed. It is uncertain, in the absence of continued intervention, whether these improvements are temporary or permanent. It is certainly possible that reperfusion injury has a late as well as an early component. If sustained improvement in myocardial salvage with surgical reperfusion can be demonstrated, the current practice which favors medical revascularization of acute infarction should be reconsidered.

The present experimental study compares the early and late outcome of medical versus surgical reperfusion in dogs after two hours of coronary occlusion simulating clinically feasible medical and surgical revascularization protocols. Flow restoration in "medically treated" animals represented successful thrombolysis or angioplasty. Surgically reperfused animals underwent 45 minutes of cardioplegic arrest consistent with performance of multiple distal coronary anastomoses. A group of control animals underwent permanent coronary ligation, representing patients not receiving early reperfusion. The timing and magnitude of the interventions were designed to parallel those currently available for the patient seen with established, ongoing ischemia.

Material and Methods

Experimental Procedure

Forty-three heartworm-free mongrel dogs (20 to 35 kg) were used in a two-stage chronic study. In the first stage, carried out under sterile conditions, the animals were premedicated with morphine sulfate, 4 mg/kg, subcutaneously and anesthesia was induced with intravenous sodium pentobarbital, 20 mg/kg, and maintained with the same agent intravenously. Endotracheal ventilation was controlled by a Bennett MA-1 volume ventilator. Adequate oxygenation and ventilation was assured by frequent arterial blood gas analyses.

The heart and great vessels were exposed through a left lateral thoracotomy. Aortic and left atrial pressures were monitored with Hewlett-Packard quartz pressure trans-

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ducers (Model 1290-A, Hewlett-Packard, Andover, MA) using fluid-filled polyethylene catheters inserted through the internal mammary artery and the left atrium, respectively. Left ventricular pressure and its first derivative (LV dp/dt) were obtained from a 7F Mikro-Tip catheter transducer (Miller Instrument Inc, Houston, TX) inserted via the proximal descending thoracic aorta. Two pairs of sonomicrometric piezoelectric crystals were implanted in the midmyocardium, perpendicular to the long axis of the left ventricle in the distribution of the left anterior descending coronary artery (LAD) and of the circumflex coronary artery (CX). The crystals were secured in place using 6-0 Prolene (Ethicon) sutures. Myocardial segment lengths were measured by a Triton sonomicrometer (Triton Technology Inc, San Diego, CA). Two atrial pacing wires, one attached to the right atrium and the other to the left atrium, were placed to enable atrial pacing at 120 beats per minute if the animal's heart rate was below that level. A Swan-Ganz catheter was inserted into the pulmonary artery for cardiac output measurements using the thermodilution method.

After instrumentation, baseline hemodynamic and functional measurements (control values) were obtained. After systemic heparinization (4 mg/kg), normothermic regional ischemia was produced for two hours by snare occlusion of the proximal LAD immediately beyond the origin of the first diagonal branch. Visible collateral vessels from the CX were also snared. A 100-mg lidocaine injection was given intravenously five minutes before occlusion, and a lidocaine infusion (1 mg/min) was administered during the period of coronary ligation and early reperfusion. Myocardial blood flows of both the normal and ischemic regions were measured by injecting radioactive microspheres (15 μm, DuPont New England Nuclear, Boston, MA) into the left atrium after 30 minutes of regional ischemia. A reference sample was obtained by withdrawing a known quantity of blood through the internal mammary artery for one minute simultaneously with injection of the microspheres [17]. Complete collection of microspheres was verified by drawing a second sample for one minute after the reference sample. Hemodynamic data and segmental length measurements were continuously monitored during the ischemic period.

The animals were divided into three groups: a permanent occlusion group (P), a medical reperfusion group (M), and a surgical reperfusion group (S). In the permanent occlusion group, the animal's LAD and its collaterals were permanently ligated with no subsequent reperfusion. This group simulates acute clinical coronary occlusion without early reperfusion. Hemodynamic and segmental length measurements were obtained after two hours of LAD ligation. In the medical reperfusion group, the LAD occlusion and snares on collateral vessels were released after two hours of ischemia to provide unmodified reperfusion with the heart in the beating, working state, simulating revascularization by thrombolytic agents and/or angioplasty. Hemodynamic and segmental contraction measurements were repeated after 30 minutes of reperfusion.

Table 1. Contents of Substrate-Enriched Blood Cardioplegia

Component	Crystalloid Content	Concentration Delivered
Blood		Hematocrit, 20%–30%
KCl	50 mEq/L	12–16 mEq/L
THAM (0.3 M)	260 mL	
Glucose	16.2 g/L	>400 mg/dL
Aspartate	10.1 g/L	12 mmol/L
Glutamate	11.0 g/L	12 mmol/L
CPD	65 mL	500–600 mmol/L
Allopurinol	0.68 g/L	1 mmol/L
pH		7.8 at 37°C
Osmolarity		370–400 mosm/L

In the surgical reperfusion group, the animals were placed on total cardiopulmonary bypass immediately before reperfusion after two hours of regional ischemia, using a 14F right-angle arterial cannula in the left subclavian artery and a single modified 34F right atrial cannula. The aorta was then clamped, and a substrate-enriched cardioplegic solution was infused for five minutes at 50 mm Hg and 37°C via a double-lumen aortic root cannula (Table 1). While the aorta was clamped, the left ventricle was vented through a left atrial catheter to avoid any distention. Simultaneously, the LAD and collateral occlusions were released. The initial warm cardioplegic reperfusate was followed by a five-minute infusion of 4°C blood cardioplegic solution of the same composition. At this time, the animal was systemically cooled to 28°C. The aorta was clamped for a total of 45 minutes, and cold blood cardioplegic replenishments were given at 20 minutes and 35 minutes at 50 mm Hg pressure for two minutes to simulate the operating conditions when multiple distal graft anastomoses are performed. Systemic rewarming of the animal began after 35 minutes of hypothermic global ischemia, and 37°C substrate-enriched blood cardioplegic solution was infused for three minutes at 50 mm Hg immediately before the aortic clamp was removed. After clamp removal, perfusion pressure was initially lowered to 50 mm Hg, and was gradually raised to 80 mm Hg over a five-minute period. The total duration of ischemia in the surgical reperfusion group was 2 hours 45 minutes (2 hours of normothermic coronary ligation and 45 minutes of hypothermic aortic clamping). The animal was then maintained on cardiopulmonary bypass for an additional 30 minutes before the heart was returned to the beating, working state for 30 minutes and repeat hemodynamic and segmental-length measurements were obtained.

After all necessary measurements were recorded, the chest incision was closed and the animals were allowed to recover. All animals received 24 hours of perioperative antibiotics with intravenous and intramuscular cephapirin sodium and three days of intramuscular morphine sulfate analgesic.

The second stage of the study occurred 1 week later. The animal was premedicated and anesthetized as for the first part of the study, the left chest incision was reopened, and left atrial, left ventricular, aortic, and Swan-

Ganz catheters, as well as atrial pacing wires, were reinserted. The ultrasonic crystals imbedded in the myocardium were reconnected to the sonomicrometer. Hemodynamic, segmental-length, and regional blood flow (using microspheres) measurements were documented. The area of left ventricle at risk for infarction was determined by reoccluding the LAD and the obvious collateral vessels (in medical and surgical animals) and injecting 35 mL of 5% Evans blue dye into the left atrium. After 10 seconds, the heart was arrested with intracardiac KCl, excised, and trimmed of atria, great vessels, and right ventricular free wall. The left ventricle was sliced into 5-mm-thick transverse sections and weighed. Each side of each slice was traced on acetate paper to define the stained (nonischemic) and unstained (ischemic) tissue. The slices were then incubated in a 1% solution of triphenyltetrazolium chloride for 30 minutes at 37°C [18]. The area of infarcted myocardium, which did not stain with triphenyltetrazolium chloride, was traced on acetate sheets. The area at risk and the area of infarct were determined by planimetry and expressed as a percent of the total left ventricular area. Infarct size is expressed as a fraction of the area at risk. After the tissue was stained for infarction, the center of the ischemic area was sampled for radioactive microsphere determinations to evaluate regional blood flow.

All experiments were performed in accordance with "The Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985).

Data Analysis

Animal data were excluded from analysis if the animal failed to complete the entire experimental protocol. Myocardial salvage was assessed by comparing the ratio of area of infarct to area at risk in the left ventricle.

Regional blood flow during acute ischemia and chronic recovery phases was estimated using the microsphere technique [17]. Transmural, epicardial, and subendocardial flows were calculated in both ischemic and normal regions by selecting representative muscle samples in the anterior (ischemic or nonstained) and posterior (normal) surfaces of the left ventricle, respectively. Ischemic flow was normalized and presented as percentage of transmural flow in the normal myocardium.

Systolic segmental shortening and pressure-length loops of the ischemic LAD and nonischemic CX regions were used to assess regional ventricular function. Percent systolic shortening was calculated as 100 × (EDL − ESL)/EDL, where EDL and ESL are end-diastolic length and end-systolic length, respectively. Pressure-length loops were constructed for each region by plotting the left ventricular pressure on the ordinate and the segmental length on the abscissa. The area within each of these loops is a quantitative estimate of work performance at this region of the left ventricle. The ratio of systolic segmental shortening or pressure-length loop area measured after ischemia or reperfusion to its counterpart before ischemia was used as an index of recovery of regional myocardial function. Stroke work index (SWI) was calculated as:

$$\frac{(\text{MAP} - \text{LVEDP}) \times \text{CO} \times 1.36}{\text{Body weight} \times \text{HR} \times 100},$$

where MAP and LVEDP are mean arterial and left ventricular end-diastolic pressures, HR is heart rate in beats per minute, and CO is cardiac output measured in milliliters per minute. Stroke work index (SWI) and LV dp/dt were used to estimate global left ventricular function.

Statistical Analysis

All values are expressed as mean ± standard error of the mean. Statistical analysis was performed using BMDP Statistical Software (BMDP Statistical Software, Inc, Los Angeles, CA) under the supervision of E. C. Hall, PhD, Department of Biometry and Statistics, Emory University. Comparison of control variables with measurements obtained during the ischemic and reperfusion periods were made with the paired Student's t test or Wilcoxon signed rank test, as appropriate. A repeated measures analysis of variance was used to evaluate the main effects of reperfusion treatment method and experimental phase and their interaction, followed by pairwise comparisons using the Bonferroni method. Unpaired t test and analysis of variance were used to compare group means. Multivariate analyses using stepwise regression were performed to evaluate the effect of treatment, regional function during ischemia, and area at risk on infarct size or regional function after 1 week of recovery. Simple linear regression was used to analyze the relationships between regional ischemic function, recovery of function, and infarct size. Probability (p) values less than 0.05 were considered to be statistically significant.

Results

Exclusions from Data Analysis

Twenty-two of 43 animals completed the two-staged study. Sixteen animals developed ventricular fibrillation and died within 30 minutes of LAD occlusion. Two additional animals fibrillated after 30 minutes but before two hours of ischemia. Twenty-five dogs completed two hours of ischemia without ventricular fibrillation. Of these 25 animals, 2 dogs in the medical reperfusion group fibrillated during the early reperfusion period. Twenty-three animals, therefore, completed stage 1 and recovered from anesthesia. Of these, 1 animal in the surgical reperfusion group died four days after stage 1 due to gastrointestinal hemorrhage and small bowel obstruction related to a congenital jejunal diverticulum discovered at autopsy. The remaining 22 dogs completed stage 2 and were included in data analysis. Seven underwent permanent LAD ligation, 8 received medical reperfusion, and 7 had surgical reperfusion.

Ischemia

Baseline hemodynamic and regional function were similar in animals of all three groups (Tables 2 and 3). Before regional ischemia was induced, the average percent systolic segmental shortening of the LAD region was 15.9% ± 2.0%, 18.7% ± 2.5%, and 15.6% ± 1.2% in the perma-

Table 2. Selected Hemodynamic Data[a]

Variable	Control	2-Hour Ischemia	30-Minute Reperfusion	1 Week
Mean aortic pressure (mm Hg)				
Permanent occlusion (n = 7)	122 ± 9	101 ± 7		114 ± 9
Medical reperfusion (n = 8)	110 ± 3	104 ± 5	96 ± 4[b]	109 ± 5
Surgical reperfusion (n = 7)	120 ± 4	102 ± 6[b]	92 ± 5[b]	106 ± 8
Left atrial pressure (mm Hg)				
Permanent occlusion (n = 7)	8.0 ± 1.5	9.3 ± 1.3		9.9 ± 2.1
Medical reperfusion (n = 8)	7.2 ± 1.4	8.4 ± 1.0	7.9 ± 1.0	6.6 ± 1.4
Surgical reperfusion (n = 7)	7.7 ± 1.6	9.3 ± 1.4	7.4 ± 1.2	8.7 ± 1.4
Max dp/dt (% control)				
Permanent occlusion (n = 7)	100	91 ± 3[c]		115 ± 9
Medical reperfusion (n = 8)	100	81 ± 3[b,c]	86 ± 2[b,c]	108 ± 8
Surgical reperfusion (n = 7)	100	77 ± 6[b]	99 ± 9	120 ± 13
Stroke work (% control)				
Permanent occlusion (n = 6)	100	65 ± 10		72 ± 9
Medical reperfusion	100 (n = 6)	73 ± 2 (n = 5)	76 ± 3 (n = 5)	105 ± 18 (n = 6)
Surgical reperfusion	100 (n = 7)	61 ± 3 (n = 4)	60 ± 4 (n = 7)	89 ± 11 (n = 6)

[a] All values in mean ± SEM. [b] Significance: $p < 0.05$ vs control. [c] Significance: $p < 0.02$ vs 1 week.

nent occlusion, medical reperfusion, and surgical reperfusion groups, respectively. Five minutes after the proximal LAD was occluded, all animals developed significant bulging (mean, −35.7% ± 5.1% of control shortening). The nonischemic CX regions maintained 95.8% ± 11.9% of control segmental shortening. Three animals had CX hyperkinesis of over 20% (2 in group P and 1 in group S). Two animals in the surgical group developed significant CX dysfunction, 18% and −61% of control shortening, respectively, in addition to LAD bulging. This pattern of regional dyskinesis continued throughout the two-hour ischemic period in all experimental subjects with little improvement. At the end of two hours, the area within the pressure length loop in the ischemic region averaged only 6.7 ± 3.5% of control levels, and stroke work index decreased by almost 35%, indicating severe myocardial dysfunction. There was no significant difference in the three groups in the response to coronary occlusion.

Early Reperfusion

Immediately after reperfusion began with unmodified blood, 2 animals assigned to the medical reperfusion treatment group sustained irreversible ventricular fibrillation and died. These 2 animals were excluded from the study. In contrast, all animals in the surgical reperfusion group had no reperfusion ventricular ectopy, and all but

Table 3. Regional Function Data

Variable	Control	2-Hour Ischemia	30-Minute Reperfusion	1 Week
LAD systolic shortening (%)[a]				
Permanent occlusion (n = 7)	15.9 ± 2.0 (100)	−1.6 ± 2.2 (−9.0 ± 16.3)	. . .	3.2 ± 1.6 (26.0 ± 14.4)
Medical reperfusion (n = 8)	18.7 ± 2.5 (100)	−5.7 ± 1.7 (−36.0 ± 10.6)	−1.2 ± 1.9 (−9.0 ± 9.2)	3.2 ± 1.2 (19.0 ± 7.1)
Surgical reperfusion (n = 7)	15.6 ± 1.2 (100)	−4.9 ± 1.8 (−29.0 ± 9.8)	2.9 ± 1.0 (17.0 ± 19.3)	8.5 ± 2.0[b] (52.0 ± 10.9)
LAD pressure-length loop area (mm Hg)[a]				
Permanent occlusion (n = 7)	248 ± 33 (100)	23 ± 11 (8.2 ± 3.8)	. . .	71 ± 24 (37.5 ± 13.1)
Medical reperfusion (n = 8)	178 ± 35 (100)	9 ± 14 (0.1 ± 5.7)	19 ± 13 (9.1 ± 5.3)	71 ± 13 (44.5 ± 7.4)
Surgical reperfusion (n = 7)	177 ± 17 (100)	24 ± 17 (13.0 ± 7.6)	64 ± 23 (33.4 ± 11.3)	115 ± 25 (65.3 ± 13.2)

[a] Numbers in parentheses are the percent of control value. [b] S vs M and S vs P, $p < 0.05$; analysis of variance, $p < 0.05$.

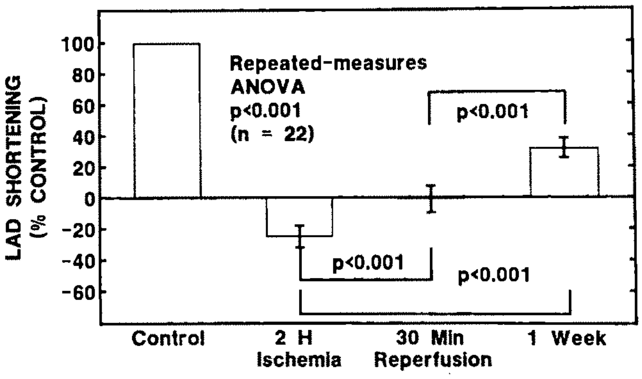

Fig 1. Regional shortening in the left anterior descending (LAD) region decreased after two hours of ischemia with significant bulging in all groups. Regional shortening improved in all three groups over 1 week after the initial LAD region damage. This improvement occurred in the group with permanent occlusion as well as in the two groups with reperfusion (see Table 3).

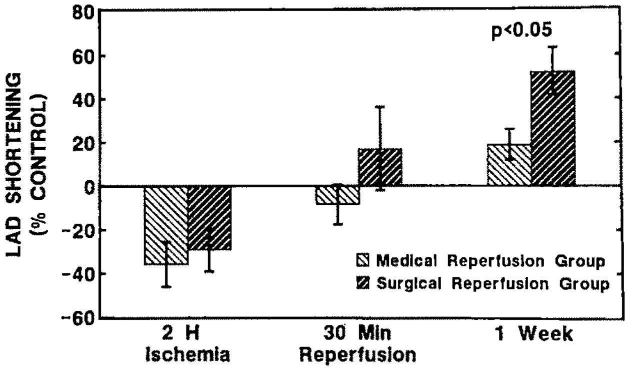

Fig 2. Recovery of left anterior descending (LAD) shortening was significantly superior in the surgical reperfusion group compared with the medical reperfusion group. In each of these two groups, regional bulging was present at the end of two hours of ischemia. After medical reperfusion, regional bulging persisted after 30 minutes of reperfusion but regional shortening occurred after surgical reperfusion. After 1 week of reperfusion, there was a significant difference in the recovery of regional shortening for the surgical group (52% of control) compared with the medical group (19% of control, $p < 0.05$*).*

1 resumed sinus rhythm spontaneously. However, segmental contraction was still depressed in both medical and surgical groups after 30 minutes of reperfusion, with the surgical group animals having slightly better (NS) LAD shortening and larger pressure loop length area (Table 3). No significant hemodynamic changes were noted between the two groups except the higher heart rate and increased cardiac output recorded in the surgical group. All animals that received simulated surgical reperfusion treatment were successfully weaned from cardiopulmonary bypass without pharmacologic agents. The animals in this group received an average of 1,400 mL of blood cardioplegia over 45 minutes.

Late Reperfusion

After the animals recovered from the initial operation, they were restudied 1 week later, and data are summarized in Tables 2 and 3. In general, regional function was significantly better compared with the measurements during ischemia and acute reperfusion (Fig 1). Global ventricular function and hemodynamic values were similar to control levels. The mean LAD segmental shortening for all 22 animals improved from −25% of control after two hours of ischemia to 32% of control ($p < 0.001$ by RMANOVA) after 1 week of recovery (Fig 1). The mean regional work performed (pressure-length loop) also improved from 17% to 49% of control ($p < 0.001$ by RMANOVA). The recovery of segmental shortening at 1 week was significantly better for the surgical group than for the medical reperfusion group (52% vs 19%, $p < 0.05$) (Fig 2).

Infarct size determination at 1 week using triphenyltetrazolium chloride staining also showed marked differences between treatment groups. Animals who suffered permanent proximal LAD occlusion had the largest infarcts, an average of 45% of the area at risk. The infarct size in the medically reperfused group was only slightly better (NS), averaging 38% of the area at risk. A dramatic improvement was observed in the surgically reperfused group, with the infarct size averaging only 19% of the area at risk ($p < 0.05$ vs. medical or permanent groups) (Fig 3).

Myocardial blood flow measurements during acute ischemia indicated the regional flows to the ischemic endocardium and epicardium at risk were reduced to 26% ± 8% and 32% ± 2% of transmural blood flow in the respective CX regions. After 1 week, the blood flow to the vulnerable endocardium improved to 45% ± 9% of normal flow, while the vulnerable epicardium received 66% ± 8% normal flow. The flow distribution and recovery were not significantly different among the three treatment groups.

Multivariate analyses were performed to evaluate the relative importance of treatment, ischemic blood flow, and area at risk as predictive variables for eventual infarct size. The treatment difference was the only significant determining factor in myocardial salvage ($F = 6.53$, $p <$

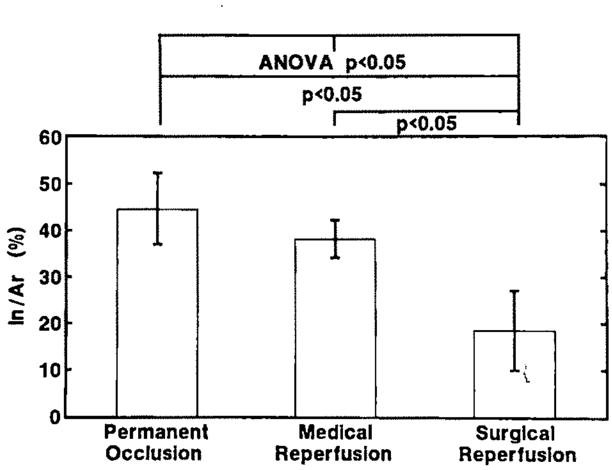

Fig 3. Infarct size determination at 1 week using staining revealed marked differences between the treatment groups. In the surgically reperfused group, the area of infarction divided by the area at risk (In/Ar) was only 19%, compared with 38% for the medical reperfusion group ($p < 0.05$) *and 45% for the permanent occlusion group* ($p < 0.05$)*.*

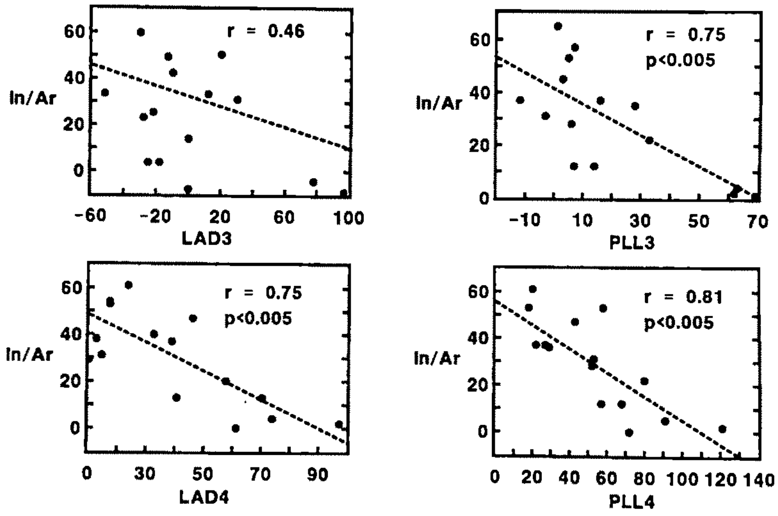

Fig 4. A search was made for a significant relationship between regional shortening or regional work and infarct size (In/Ar, area of infarction divided by area at risk) in the 15 animals that were reperfused either medically or surgically. There was a poor correlation between left anterior descending (LAD) region shortening after 30 minutes of reperfusion (LAD 3) and infarct size. A significant relationship was observed between infarct size and LAD region shortening at 1 week (LAD 4), pressure-length loop area at 1 week (PLL 4) or pressure-length loop area after 30 minutes of reperfusion (PLL 3).

0.05). Likewise, treatment difference was found to be the most important factor affecting recovery of LAD segmental systolic shortening ($F = 5.47$, $p < 0.05$).

Simple linear regression used the data from the 15 reperfused animals to analyze the relationship between global or regional myocardial function after reperfusion and the ultimate infarct size at 1 week. A significant relationship was observed both between 1-week segmental shortening and infarct size and between 1-week pressure-length loop area and infarct size (Fig 4). Regional performance after 30 minutes of reperfusion in the form of pressure-length loop area also showed a significant correlation with the eventual infarct size.

Comment

Techniques of reperfusion used by the invasive cardiologist offer substantially less flexibility than those currently available to the surgeon. In addition to the restoration of flow to acutely infarcting myocardium, surgical techniques allow precise control of the conditions of reperfusion and modification of the reperfusate [3–16]. This modification appears to favorably influence degenerative structural and biochemical processes in reversibly injured myocardium. Changes accompanying reperfusion that may exacerbate preexisting ischemic injury include the development of intracellular acidosis and calcium accumulation, myocyte swelling, the explosive production of oxygen-derived free radicals, the adhesion of granulocytes, and the delayed restoration of substrates for adenine nucleotide synthesis [1, 2, 19–21]. Previous investigations, presented primarily in the surgical literature, have documented an improvement in the acute recovery of ischemic myocardium with surgical reperfusion [3–16].

These previous investigations, using models of regional as well as global ischemic injury, have led to the development of a supplemented blood cardioplegic solution as the initial reperfusate, adopted for use in the present study [10]. Components of this cardioplegia are directed against specific aspects of the pathophysiology of reperfusion injury. Red blood cells improve oxygen delivery and, as particulate material, maintain capillary patency and counteract the "no-reflow" phenomenon. Reduction of calcium concentration by chelation assists in restoring intracellular calcium homeostasis. An alkaline pH reverses acidosis and enhances enzyme function. Electrical arrest prevents initial utilization of energy in the performance of contractile work. Glucose provides substrates for energy production. Allopurinol is a xanthine oxidase inhibitor and decreases oxygen radical production [22, 23]. Glutamate and aspartate, by replenishing Krebs' cycle intermediates, augment oxidative metabolism under aerobic conditions. Other investigations have emphasized the importance of unloading of the ventricle in myocardial recovery after reperfusion [6, 11, 13]. It is clear, from earlier studies, that the use of these surgical reperfusion techniques leads to improved regional function early after ischemia. However, earlier studies have not answered the critical questions. Do these surgical reperfusion techniques prevent reperfusion injury or simply delay the injury? Is the improvement in regional function temporary or permanent?

As one considers the recovery of myocardium after ischemic injury, another important question is evident. There is ample evidence that recovery after ischemia requires a prolonged time interval. Energy stores may remain depressed for 1 week after temporary ischemia, and recovery of regional function is similarly delayed [19, 20, 24]. Perhaps these methods of surgical reperfusion accelerate the recovery that was going to occur in any case. The clinical argument favoring surgical reperfusion becomes much stronger if the improvement in regional function and infarct size, which has been demonstrated in acute experiments, can be extended to a chronic experimental model.

The experimental model chosen for this study was a canine LAD infarction using pentobarbital anesthesia. This particular model was chosen because it allowed comparison with the acute studies extensively conducted by others, and because of the favorable experience of this laboratory with canine models in both acute and chronic preparations. Because comfortable survival of the animal was a priority, the sterile first stage of the study was intentionally kept simple and short. For example, a thermal dilution technique was used to measure cardiac output rather than an ascending aortic flow probe, which would require extensive dissection and then redissection of the ascending aorta. The LAD was ligated and a sufficient number of additional collaterals were snared to achieve a visible, measurably bulging area of infarction. This bulging occurred during at least one portion of systole but often not throughout systole. Therefore, the pressure-length loop area during ischemia was often positive even though bulging occurred at end systole (see Table 3, systolic shortening compared with pressure-length loop area). All animals were heparinized before ligation of the LAD in an attempt to minimize possible deleterious effects of thrombosis in the vasculature of the area at risk. This procedure was felt to be justified because, in human infarction, the distal vasculature is generally not thrombosed in the first few hours of infarction.

This study examined both the early and late results of reperfusion using strategies available to the clinician. Other experimental approaches to reduction of reperfusion injury have initiated specific therapy in the form of free-radical scavengers or calcium channel antagonists before the onset of ischemia, or have used ischemic intervals incapable of producing myocardial infarction. Our protocol allowed no treatment before or during the ischemic period other than conventional antiarrhythmic therapy. A two-hour period of ischemia was chosen to represent the minimum duration likely to occur clinically with any method of revascularization. At the completion of ischemia, there were no functional or hemodynamic differences among the groups that underwent medical or surgical reperfusion or permanent coronary ligation. Reduction of coronary flow to the LAD region uniformly produced acute myocardial discoloration, severe bulging, and a corresponding reduction in regional work. This degree of ischemia was ensured by the snaring of collateral vessels until the bulging obtained was visible as well as measurable with the sonomicrometer. Despite the severity of regional ischemia, there was little change in global hemodynamics among the three groups, as the reduction in work by the anterior descending region did not severely compromise global left ventricular function. It follows that the animals in this study correspond to patients who sustain a substantial infarct yet have sufficient myocardial reserve for survival.

Our data obtained early after reperfusion are distinguishable from those of previous reports, which demonstrated significantly superior acute functional recovery for surgically reperfused animals [10]. This may have been due to the relatively small number of animals in this chronic study, among which substantial variability was noted. There was improvement among both medically and surgically reperfused animals in regional shortening and work production (Table 3). More surgically treated animals recovered net systolic shortening early after reperfusion. In addition, no ventricular ectopy occurred after completion of surgical reperfusion, and all surgical animals recovered sinus rhythm spontaneously.

After 1 week of reperfusion a significant improvement in regional function was observed in all groups, including those animals who underwent permanent coronary ligation. Our data support the existence of stunned, yet viable myocardium within a region of infarction that is capable of gradual functional improvement [19, 20, 24]. This recovery may be dependent on a gradual increase in collateral flow to reversibly injured cells. There may also be a contribution from the stiffening of adjacent, nonviable myofibrils.

In our model, the recovery in function among animals undergoing simulated medical reperfusion was equivalent to the recovery observed in animals with permanent coronary ligation. Surgically reperfused animals, however, experienced an improvement in regional shortening superior to both medically reperfused and nonrevascularized animals, which was statistically significant despite the small numbers of animals in each group (52% ± 29% of control vs 19% ± 20%, 26% ± 38%; $p < 0.05$). These data comparing the chronic sequelae of medical and surgical reperfusion suggest that altering the conditions of early revascularization led to considerable benefit, whereas in this model the simple restoration of flow offered little advantage over permanent occlusion.

Measurement of infarct size provides the most tangible evidence of myocardial salvage. Surgically treated animals 1 week after reperfusion had, relative to the area at risk, infarcts that were half the size of those in animals medically reperfused or permanently ligated (18.6% ± 8.6% vs 38.3% ± 4.1%, 44.7% ± 7.7%; $p < 0.05$). Recent evidence suggests that conventional triphenyltetrazolium chloride staining in acute studies yields results discordant with observed functional recovery [21, 25]. However, our data indicate that at 1 week cellular survival is established, with the result that infarct size more closely parallels measurements of regional function (Fig 4).

There are limitations to extrapolation of these experimental results to humans. The LAD region underwent a two-hour period of ischemia, within the known limits of postischemic myocardial recovery [20, 24, 26]. Although late myocardial salvage after surgical reperfusion was improved in this study, the duration of ischemia beyond which the advantage of surgical reperfusion dissipates is uncertain, although improvement has been demonstrated after as long as six hours of ischemia [12]. The size of infarcts in this study was smaller than might be expected in patients. Although severe anterior wall ischemia was produced by occlusion just beyond the first LAD diagonal branch, the actual area at risk averaged just 25% of the left ventricular mass. Extrapolation of our results may not be valid for very large infarcts, but the data lend support to preferential surgical reperfusion of patients with survivable infarcts. Surgical treatment for such patients is complex and does carry, as seen in one of the animals in the present study, a certain operative mortality. The clinician must weigh this risk against a potential reduction in infarct size of approximately 50%. Despite the complexity and inherent morbidity of surgical reperfusion, several series have shown the mortality with surgical intervention for acute myocardial ischemia to be as low as or lower than that with medical treatment [27–30].

Our results demonstrate that modification of the conditions of initial reperfusion can profoundly influence the ultimate level of myocardial salvage. In our model, medical reperfusion simulating thrombolysis or angioplasty produced late results similar to the sequelae of permanent coronary ligation. However, surgical reperfusion with cardioplegic arrest salvaged half of the cells that died with medical reperfusion. We feel that clinical trials evaluating controlled surgical reperfusion of acute myocardial infarction are most appropriate.

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Intraoperative Ultrasonic Imaging of the Ascending Aorta

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Embolization of atherosclerotic material from the ascending aorta resulting from placement of cannulas or vascular clamps is a major cause of stroke during cardiac surgical procedures. In an effort to identify atherosclerotic disease of the ascending aorta which might predispose to embolization, intraoperative B-mode ultrasonography was performed in 50 patients. The aorta was imaged from the aortic annulus to the origin of the innominate artery in transverse and longitudinal views. The results were compared with visual and tactile examination of the aorta for the presence of atherosclerosis. Ultrasonic imaging demonstrated atherosclerotic disease in 29 patients (58%). Visual examination and palpation identified atherosclerosis in 12 patients (24%). The amount and location of plaque was sufficient to require a change in the site of arterial cannulation or the proximal vein graft anastomoses or the technique of cardiopulmonary perfusion in 12 of the 50 patients (24%). All 12 patients were 65 years of age or older. Palpation underestimates the presence of atherosclerotic disease in the ascending aorta. Intraoperative ultrasonography accurately identifies patients with atherosclerotic disease of the ascending aorta. This allows the surgeon to modify cannulation, perfusion, and operative techniques to reduce the risk of perioperative stroke due to the embolization of atherosclerotic debris from the ascending aorta.

(Ann Thorac Surg 1989;48:339–44)

Stroke is a serious and disabling complication of cardiac surgical procedures. A major cause of perioperative stroke is embolization of atherosclerotic material from the ascending aorta, which may result from insertion of perfusion cannulas, placement of clamps on the ascending aorta, or palpation of the ascending aorta [1]. Palpation of the aorta may identify areas of calcification or marked thickening, but may not identify lesser degrees of calcification or thickening or areas of soft, "cheesy" atheroma. In an effort to accurately identify atherosclerotic disease of the ascending aorta, a technique using intraoperative B-mode ultrasonic imaging of the ascending aorta was evaluated.

Material and Methods

Fifty patients undergoing cardiac surgical procedures using cardiopulmonary bypass were studied during a 9-month period (September 1987 to May 1988). The mean age of the patients was 70 years (range, 47 to 83 years) and 28 (56%) were men. The patients were not consecutive, due to equipment availability, and there was a degree of selectivity in that efforts were made to image patients felt to be at increased risk for atheroembolism.

The operative procedures performed are shown in Table 1. Forty-three patients had coronary artery bypass grafting, 2 patients had coronary artery bypass grafting and left ventricular aneurysmectomy, 2 patients had isolated valve replacement (one aortic, one mitral), 2 patients had ascending aorta/aortic arch replacement, and 1 patient had coronary artery bypass grafting and concomitant right carotid endarterectomy.

After median sternotomy, mobilization of the internal mammary artery, if used, and suspension of the heart in a pericardial cradle, the aorta was examined visually and by palpation. The extent and location of calcification or thickening thought to be present was recorded. Ultrasonic imaging of the ascending aorta was then performed using either a Hewlett-Packard 77020A phased array system with a 5-MHz transducer with a 4-cm sonolucent standoff (Hewlett-Packard Company, Medical Products Group, Andover Division, Andover, MA), or a Medasonics 210 DX Vasculab with a 7.5-MHz transducer (Medasonics, Mountain View, CA) without a standoff. The transducer was placed in a sterile plastic sleeve containing conducting gel and placed directly on the ascending aorta. The aorta was imaged in transverse and longitudinal views from the aortic annulus to the origin of the innominate artery (Fig 1–3). The scans were recorded on standard VHS video tape and were reviewed by the surgeon and a cardiologist in the operating room. The results of the scans were compared with the visual and digital findings. Based on the results of the ultrasonic imaging, modifications of the usual cannulation and proximal graft anastomotic sites and perfusion protocols were made by the surgeon, if indicated. The operative procedures were then

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Table 1. Operative Procedures in the 50 Patients

Procedure	No. of Patients	%
Coronary artery bypass grafting	43	86
Coronary artery bypass grafting and left ventricular aneurysmectomy	2	4
Valve replacement	2	4
Ascending aorta/aortic arch replacement	2	4
Coronary artery bypass grafting and right carotid endarterectomy	1	2

performed. The patients were evaluated postoperatively for evidence of perioperative stroke or wound infection.

Results

By visual and digital examination of the aorta, 38 patients (76%) were thought to have a normal aorta, and 12 patients (24%) were thought to have an abnormal aorta. By ultrasonic imaging, 21 patients (42%) had normal aortas and 29 patients (58%) had abnormal aortas. This included the 12 patients with an abnormal aorta by palpation and 17 patients with a normal aorta by palpation (Table 2). The intraoperative decisions resulting from detection of atherosclerotic material are shown in Table 3. Twelve of the 17 patients (71%) with a normal aorta by palpation had only small amounts of plaque or plaque located in areas that would not affect the conduct of the

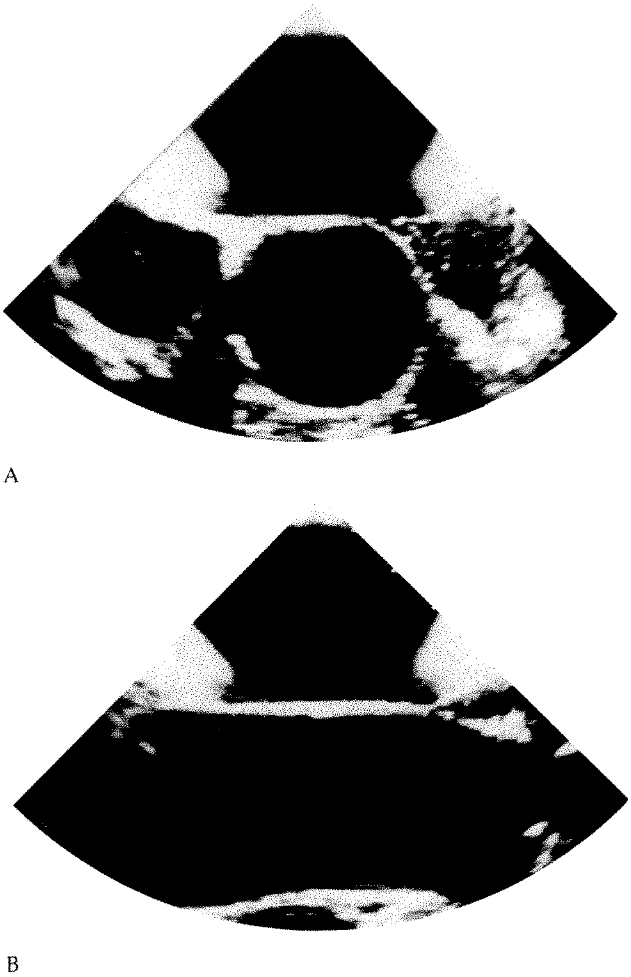

Fig 1. (A) Transverse ultrasonic image of the ascending aorta demonstrating normal aortic wall and no intraluminal echogenic material. (B) Longitudinal ultrasonic imaging of the ascending aorta showing normal aortic wall and no intraluminal echogenic material.

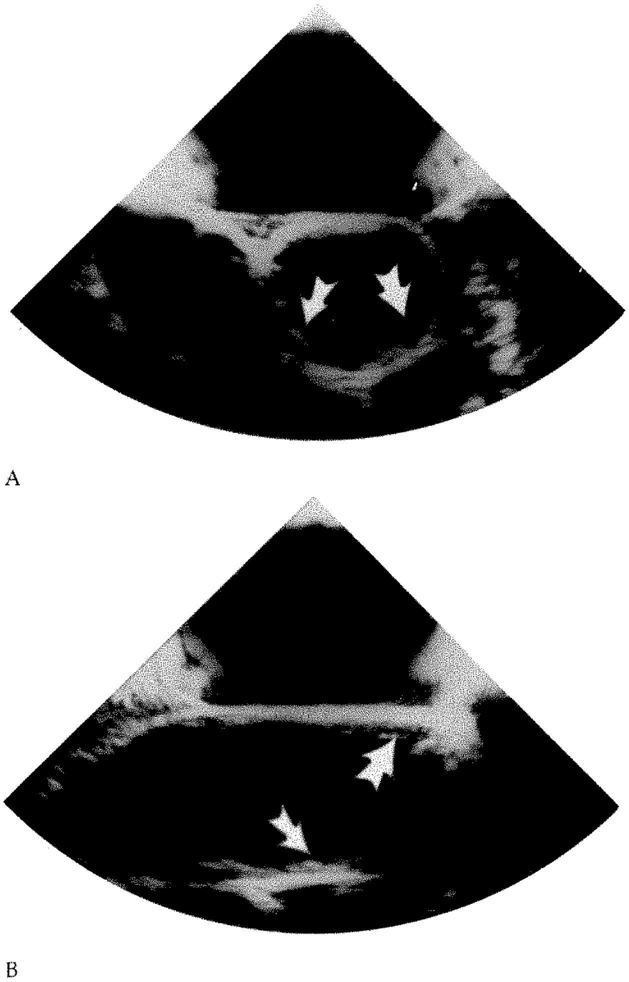

Fig 2. (A) Transverse ultrasonic imaging of the ascending aorta showing thickened aortic wall and intraluminal echogenic material (arrows). *(B) Longitudinal image of the same aorta demonstrating thickened aortic wall and intraluminal echogenic material* (arrows).

Table 2. Comparison of Palpation and Ultrasonic Imaging for Detection of Atherosclerotic Disease of the Ascending Aorta (n = 50)

	Palpation		Scan	
Result	No. of Patients	%	No. of Patients	%
Normal	38	76	21	42
Abnormal	12	24	29	58

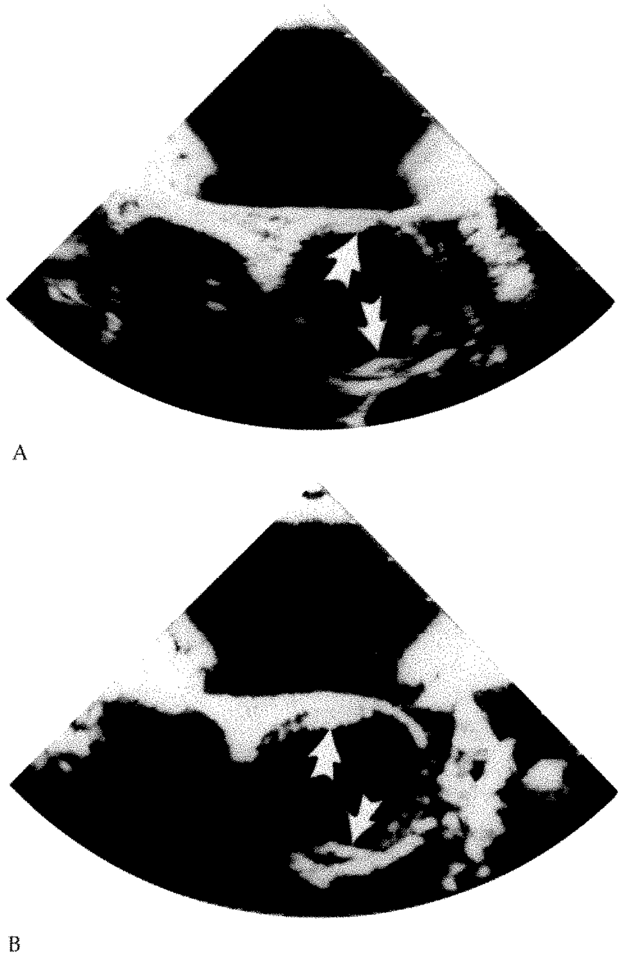

Fig 3. Transverse ultrasonic image of the ascending aorta showing thickened aortic wall and large amount of intraluminal echogenic material (arrows).

operation (eg, origin of the innominate artery, aortic root). Five of the 12 patients (42%) with an abnormal aorta by palpation had similar findings on ultrasonic imaging. No modifications in techniques were made in these 17 patients. The remaining 12 patients (5 with a normal aorta and 7 with an abnormal aorta by palpation) had plaque of sufficient quantity or in locations such that a change in cannulation or perfusion techniques was required.

Table 3. Intraoperative Decisions in Patients With Abnormal Scan

Intraoperative Decision	Palpation Normal (n = 17)	Palpation Abnormal (n = 12)	Total (n = 29)
Plaque insignificant/ignored	12	5	17
Plaque detected with resulting change in cannulation/perfusion technique	5	7	12

Anatomically, the atherosclerotic plaque was located in the anterior half of the circumference of the aorta in 22 of the 29 patients with abnormal scans (76%), and in all 12 of the patients in whom technical changes were made based on the scan findings. In addition, the amount of disease located posteriorly was much less than the amount located anteriorly. Plaque was more prevalent anteriorly in patients with disease located in the upper half of the ascending aorta (17/18; 94%) compared with patients with disease in the lower half of the aorta (5/11; 46%). Four patients had disease involving the entire length of the ascending aorta, 2 of whom had a "porcelain aorta" with disease involving the entire circumference of the aorta and 2, disease located in the anterior half of the aortic circumference (Fig 4).

The usual sites of insertion of the aortic cannula and the cannula for infusion of cardioplegic solution and the sites for the proximal saphenous vein graft anastomoses are shown in Figure 5. The changes in cannulation and in perfusion techniques resulting from the scan findings included relocation of the arterial or cardioplegic cannulation site in 6 patients, use of femoral cannulation in 2 patients, and use of femoral cannulation with hypothermic circulatory arrest and ascending aortic replacement or ascending aortic endarterectomy with patch aortoplasty without the use of vascular clamps (open technique) in 4 patients (Fig 6). Twelve of the 50 patients (24%) had some technical change made based on the findings of the ultrasonic imaging (Table 4). These 12 patients were 65 years of age or older, and they comprised 37% of the 27 patients in this age group (Table 5).

There were no wound infections in the patients studied

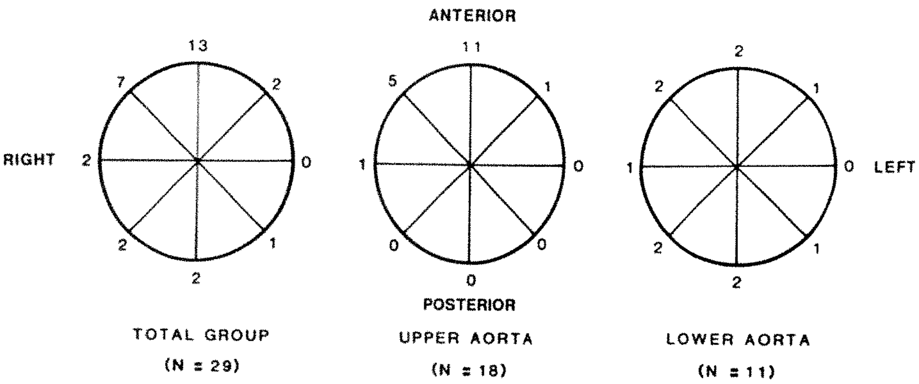

Fig 4. Anatomical location of the atherosclerotic disease in the ascending aorta as documented by ultrasonic scanning. The 4 patients with near or total circumferential disease involving the entire ascending aorta were counted in the anterior, upper aorta group.

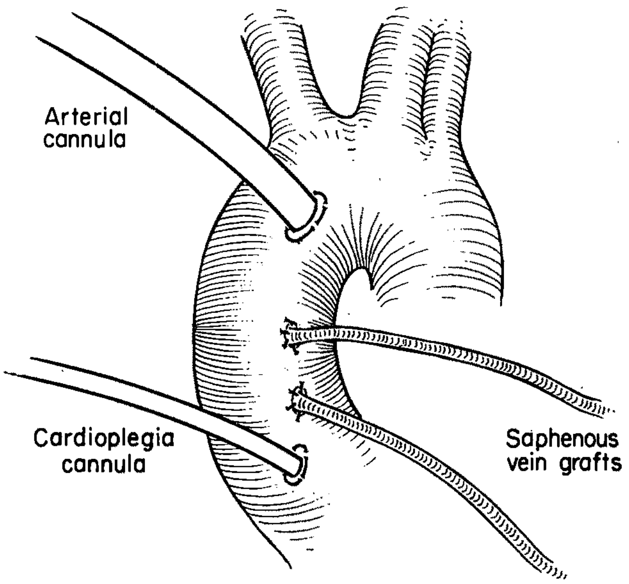

Fig 5. Usual sites of placement of the arterial and cardioplegic cannulas and the proximal anastomoses of saphenous vein grafts.

and there was one stroke (2%). This occurred in the patient who had concomitant coronary artery bypass grafting and right carotid endarterectomy. This patient had bilateral internal carotid artery stenoses greater than 95% and a normal scan of the ascending aorta. The cerebral infarct occurred in the left hemisphere, contralateral to the side of the endarterectomy.

Comment

Stroke occurring during cardiac surgical procedures using cardiopulmonary bypass has several causes. These include air embolus from the cardiopulmonary bypass circuit, intracardiac air after cardiotomy for venting or operative procedures, intracardiac thrombus, cerebrovascular occlusive disease with resultant embolization or cerebral hypoperfusion, and embolism of atheromatous material from the ascending aorta and aortic arch [2]. Atheroemboli from the ascending aorta are usually related to the placement of cannulas for cardiopulmonary bypass or vascular instruments and have been reported to occur after palpation of the ascending aorta [1].

The incidence of stroke after cardiac surgical procedures is increased in elderly patients [3] and observational data would suggest the elderly have an increased incidence of more severe atherosclerotic disease, particularly in the ascending aorta. Complications related to the diseased ascending aorta have been demonstrated to be the primary cause of unexpected death after coronary artery bypass grafting [4]. As greater numbers of elderly patients undergo cardiac surgical procedures, the risk of neurological complications, including those resulting from embolization of atheroma from the ascending aorta, may increase. In our overall experience (unpublished data), one third of perioperative strokes are related to atherosclerotic disease of the ascending aorta.

Numerous techniques have been introduced in an attempt to reduce the frequency of this complication. These include (1) placement of proximal saphenous vein graft anastomoses on the innominate or internal mammary arteries [5, 6], (2) use of an intraluminal balloon catheter rather than an aortic cross-clamp for aortic occlusion [7, 8], (3) modification of vascular instruments used to clamp

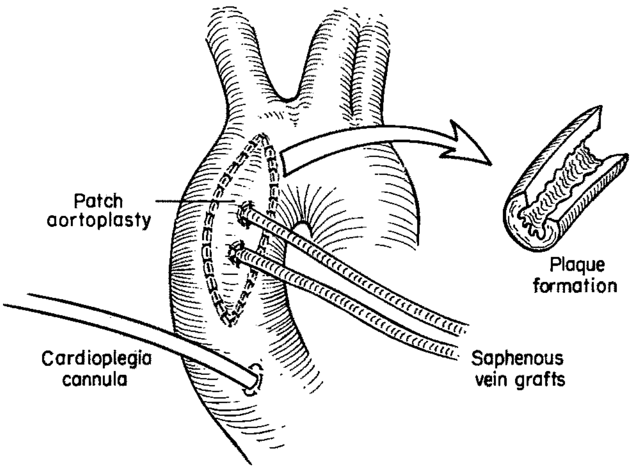

Fig 6. More lateral and inferior placement of the cardioplegia cannula and a longitudinal incision in a diffusely atherosclerotic aorta with patch angioplasty. The vein grafts are anastomosed to the Dacron patch. The arterial cannula is placed in the femoral artery.

Table 4. Changes in Cannulation and Perfusion Techniques

Change	No. of Patients	%
Relocation of aortic cannula	6	12
Femoral artery cannulation	2	4
Femoral artery cannulation with profound hypothermia, total circulatory arrest, and ascending aortic replacement or patch aortoplasty	4	8
Total	12	24

Table 5. Results of Aortic Scanning According to Age (n = 50)

Age	No. of Patients	Changes in Cannulation or Perfusion: No. of Patients	%
<65 yr	23	0	0
≥65 yr	27	12	37

the aorta [9], (4) performance of the cardiac procedure using hypothermic fibrillatory arrest to avoid placement of clamps on the ascending aorta [10], and (5) ascending aortic endarterectomy and patch aortoplasty or ascending aortic replacement with hypothermic circulatory arrest without the use of vascular clamps [1].

Before the problem can be managed, it must first be identified. The "egg-shell" or "porcelain" aorta can usually be identified by palpation of the aorta. However, focal or segmental areas of calcification or thickening may be present, and the surgeon cannot be certain if the soft areas can be cannulated or clamped without dislodgement of atherosclerotic debris. Identification of the aorta containing soft, friable atheroma can be even more difficult. The disease may not be palpable, and palpation may dislodge atheromatous material. Often, this type of aorta is not recognized until clamps have been placed and aortotomies made. By this time, embolization has usually already occurred.

Ultrasonic imaging eliminates the need for digital palpation of the aorta, which has been implicated as a cause of atheroembolization [1]. Minimal pressure is placed on the aorta with the ultrasound probe, and in this study no neurological abnormalities related to the probe were observed. The technique is simple and rapid, adding only a few minutes to the operative procedure. Interpretation of the scans is relatively straightforward and can be done by the surgeon after an initial training period. Interpretation is very similar to that performed in the imaging of peripheral arteries, but easier because no Doppler analysis is required.

Our group has extensive experience using ultrasonic techniques to detect and characterize atherosclerosis in the peripheral vessels [11]. Thus, it was a logical extension to use B-mode imaging intraoperatively to evaluate the ascending aorta. The focal length of most commercially available ultrasonic probes prevents adequate visualization of the anterior wall of the aorta. Use of a sonolucent standoff eliminates this problem. The 5-MHz probe provides excellent resolution of intraluminal detail, although a 7.5-MHz probe may be better. The Medasonics probe, because of the higher frequency and shorter focal length, was used without a standoff, and although this provided adequate images, use of a standoff appeared to be more optimal.

The modifications in operative techniques can be relatively minimal (relocation of the arterial cannula on the ascending aorta or to the femoral artery) or extensive (hypothermic circulatory arrest with endarterectomy or graft replacement of the ascending aorta). Profound hypothermia and circulatory arrest may be associated with increased risks in the elderly patient. However, we have not found this to be the case, either among the patients in this study or in other patients undergoing ascending aortic or aortic arch replacement for aneurysmal disease. Similar findings have been reported by Culliford and associates [1]. The risk of stroke may be lower with the use of hypothermic circulatory arrest than with cannulation and clamping of the diseased aorta.

The anatomical location of disease in this study differed from that reported by Tobler and Edwards [12]. They found very little disease posteriorly in the lower half of the aorta, but there were substantial amounts of plaque located posteriorly in the upper half of the aorta. In our study, no posterior plaque was found in the upper half of the aorta, and very little posterior plaque in the lower half of the aorta. Those patients requiring a technical change had disease located anteriorly with the exception of the 2 patients with circumferential disease. The smaller number of patients in our study may account for some of the differences, but the technique of evaluation (ultrasonic imaging versus gross pathological examination) is probably the major factor. Evaluation of larger numbers of patients undergoing cardiac surgical procedures will be necessary to determine the frequency of atherosclerotic disease of the ascending aorta. The incidence will likely be related to the age of the patients, and similarly, the percentage of patients requiring changes in cannulation or perfusion techniques will also be related to age.

In summary, intraoperative ultrasonic imaging identifies atherosclerotic disease of the ascending aorta. It appears to be more accurate than digital palpation. It adds little time to the operative procedure and does not increase the risk of stroke or infection. When clinically significant atherosclerotic disease is present in the ascending aorta, intraoperative imaging permits the surgeon to modify cannulation, perfusion, and operative techniques to minimize the risk of stroke from atheroembolism. Use of the technique may reduce the risk of perioperative stroke in cardiac surgical patients, particularly in the elderly. Studies in larger numbers of patients or randomized trials will be necessary to determine if the technique significantly reduces the incidence of atheroembolic stroke when compared with conventional operative techniques.

We thank Carla Kelley, Pat Renicke, and Becky Recar Nappier for technical assistance in the performance of the scans, and Lou Oxford for secretarial assistance in the preparation of the manuscript.

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Notice From the Southern Thoracic Surgical Association

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association will be held at the Phoenician Golf and Tennis Resort, Scottsdale, AZ, November 9–11, 1989. There will be a $155 registration fee for the Scientific Session for nonmember physicians except for guest speakers, authors and coauthors on the program, and residents. There will be a $50 registration fee for attendees of the Postgraduate Course, which will be held the morning of Thursday, November 9, 1989. The Postgraduate Course will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Advance registration forms, hotel reservation cards, and details regarding transportation arrangements will be mailed to Association members. Nonmembers should write to the Secretary-Treasurer, Gordon F. Murray, MD.

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Aortic Valve and Left Ventricular Outflow Tract Replacement Using Allograft and Autograft Valves: A Preliminary Report

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A comparison of allograft and autograft (pulmonary) replacement of the aortic valve has, to our knowledge, not been done in America. Fifty-seven patients (age range, 2 to 70 years; mean age, 30 years) underwent 59 operations for replacement of the aortic valve (20) or entire left ventricular outflow tract (39) using autograft (35) or allograft (24) valves. Many had undergone a previous operation (25) or had concomitant procedures (13). Postoperative mortality was 8.5% (5/59). Two deaths occurred in the allograft group and three in the more complex pulmonary autograft group. One late death occurred. One autograft was replaced with an allograft 7 months postoperatively for severe aortic regurgitation. There have been no episodes of either endocarditis or thromboembolism. Forty-nine of 51 survivors are in New York Heart Association class I. Preliminary results suggest that congenital or acquired disease of the left ventricular outflow tract and aortic valve can be safely and effectively treated with either allograft or autograft valve transplantation.

(Ann Thorac Surg 1989;48:345–9)

Reconstruction and replacement of the aortic valve is complicated at present by lack of an ideal substitute. Tissue valves suffer deterioration from primary tissue valve failure, and mechanical prostheses carry a finite risk of thromboembolic complication [1, 2]. Both are subject to increased infectious complications. To this end, we have sought to alleviate these problems by allograft and autograft (pulmonary) replacement of the aortic valve, which has been made possible by improvements in cryopreservation techniques that allow long-term storage of viable allograft valves [3].

Material and Methods

Patient Population

Fifty-seven consecutive patients undergoing replacement of the aortic valve or entire left ventricular outflow tract using allograft or autograft techniques were reviewed. Preoperative variables examined included age, sex, valve lesion, previous cardiac operation, concomitant procedure, presence of endocarditis, New York Heart Association classification, echocardiogram, and type of operation (homograft or autograft) (Table 1). We also examined the specific technique used: cylinder [4] versus root replacement [5]. The technique used was dictated by the nature of the disease and the surgeon's preference, and was not randomized.

The mean age in our series was 30 years. Predominant sex was male, with a ratio of 2:1. Indications for operation were pure aortic stenosis in 17 patients (12 congenital), aortic insufficiency without stenosis in 17 (2 congenital), and mixed aortic stenosis and insufficiency in 21 (9 congenital). The other 4 patients included 1 patient with Marfan's syndrome, 1 patient with type I aortic dissection, 1 child with aortic aneurysm after a Konno procedure, and 1 patient with an ascending pseudoaneurysm after a Bental procedure. Twenty-five patients had undergone at least one previous cardiac operation. Seven of these patients had at least two operations. Sixteen children had undergone aortic commissurotomy, 7 had an aortic valve replacement, 3 underwent aortic and mitral valve replacement, and 2 had Bental and Konno procedures. Eight patients had preoperative diagnosis of aortic valve endocarditis. Coronary artery bypass was performed in 6 of our patients and mitral valve repair or replacement in 7.

Homograft Preservation

Homograft preservation was accomplished in a manner similar to that described by O'Brien and colleagues [3]. We maintain prompt retrieval of cadaveric tissue (within 12 hours of death), followed by 24 hours of antibiotic sterilization. Valves are then placed in culture media with fetal calf serum and dimethylsulfoxide at 4°C. After sterile packaging, the tissue undergoes controlled rate freezing. A liquid nitrogen refrigerator allows long-term storage at −196°C.

Surgical Technique

Left ventricular outflow tract reconstruction was completed using both homograft and autograft (pulmonary) valves with cylinder (intraaortic) technique and as a root replacement with coronary reimplantation. Figure 1

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Table 1. Preoperative Variables

Variable	Value[a]
Age (yr)	2–70 (mean, 30)
Sex	
M	38
F	19
Valve lesion	
AS	17 (12 congenital)
AI	17 (2 congenital)
AS/AI	21 (9 congenital)
Other	4
Previous operation	19
Aortic endocarditis	8
Concomitant procedures	
CABG	6
MVR	7
Preoperative NYHA class	
I	12
II	30
III	10
IV	5
Type of operation	
Autograft	35
Homograft	24
Operative technique	
Cylinder	20
Root replacement	39

[a] Except for age, all values are number of patients.

AI = aortic insufficiency; AS = aortic stenosis; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; NYHA = New York Heart Association.

shows the technique for harvesting the pulmonary autograft. Initially, the pulmonary artery is opened anteriorly just inferior to the bifurcation and superior to the commissures. The pulmonary valve is inspected and, if it is a normal three-leaflet valve, the artery is transected distally. The right ventricular conus is then opened inferior to the pulmonary annulus, and with the valve visualized, the dissection is completed. A potential hazard exists of injury to the left anterior descending coronary artery or its first septal branch, which lie in close proximity to the pulmonary artery posteriorly [6].

To perform a cylinder autograft, the aorta is opened in an oblique fashion into the noncoronary sinus. The valve is triangulated with sutures placed at the midpoint of each sinus (Fig 2A). With the valve suspended for optimal visualization, interrupted 4-0 polypropylene sutures are placed circumferentially and the autograft is then seated and invaginated while sutures are tied (Fig 2B). An important step is suspension of the autograft commissures well into the native aorta (Fig 2C), usually 4 to 5 mm above the patient's commissures. An error in suspension will invariably lead to aortic insufficiency. With the commissures appropriately suspended, the autograft is trimmed below each coronary ostium and sewn to the native aorta with continuous 4-0 polypropylene sutures (Fig 2D). The aortotomy is then closed from the noncoronary sinus. Right ventricular outflow tract reconstruction is then accomplished with a cryopreserved pulmonary homograft. The proximal anastomosis is completed first with 4-0 polypropylene, followed by the distal anastomosis, which is also sewn with 4-0 polypropylene.

Root replacement is similar in harvesting of the pulmonary autograft. The native aorta is then opened and trimmed to preserve each coronary ostium as a "button" and to preserve the native commissures. The pulmonary autograft is then sewn with 4-0 polypropylene sutures to the left ventricular outflow tract by interrupted or continuous technique. With this completed, an opening is made in each appropriate sinus for reimplantation of the left and then the right coronary arteries with 6-0 polypropylene. The distal aortic anastomosis is completed with continuous 4-0 polypropylene suture. The right ventricular outflow tract is reconstructed as described previously. A completed pulmonary autograft performed as a root replacement is shown in Figure 3.

Results

The 57 patients evaluated (age range, 2 to 70 years; mean age, 30 years) underwent 59 operations between November 1985 and October 1988. These 57 procedures included 35 done as a pulmonary autograft with homograft reconstruction of the right ventricular outflow tract (32 pulmonary homografts, three aortic homografts), and 24 performed using cryopreserved cadaveric homografts (22 aortic homografts, two pulmonary homografts). There were five perioperative deaths (5/59, 8.5% mortality; Table 2). Two (2/24, 8.3% mortality) occurred in the group receiving homograft valves. Three perioperative deaths (3/35, 8.6% mortality) occurred in the autologous group undergoing the more extensive pulmonary autograft procedure.

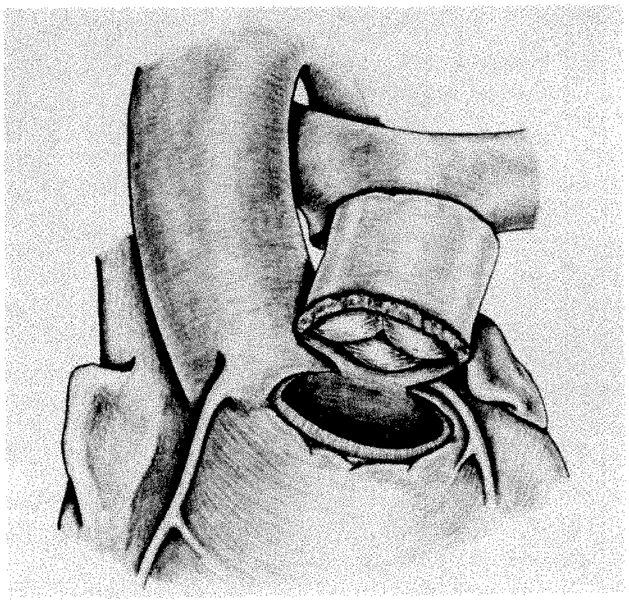

Fig 1. Technique for harvesting the pulmonary autograft from the right ventricular outflow tract.

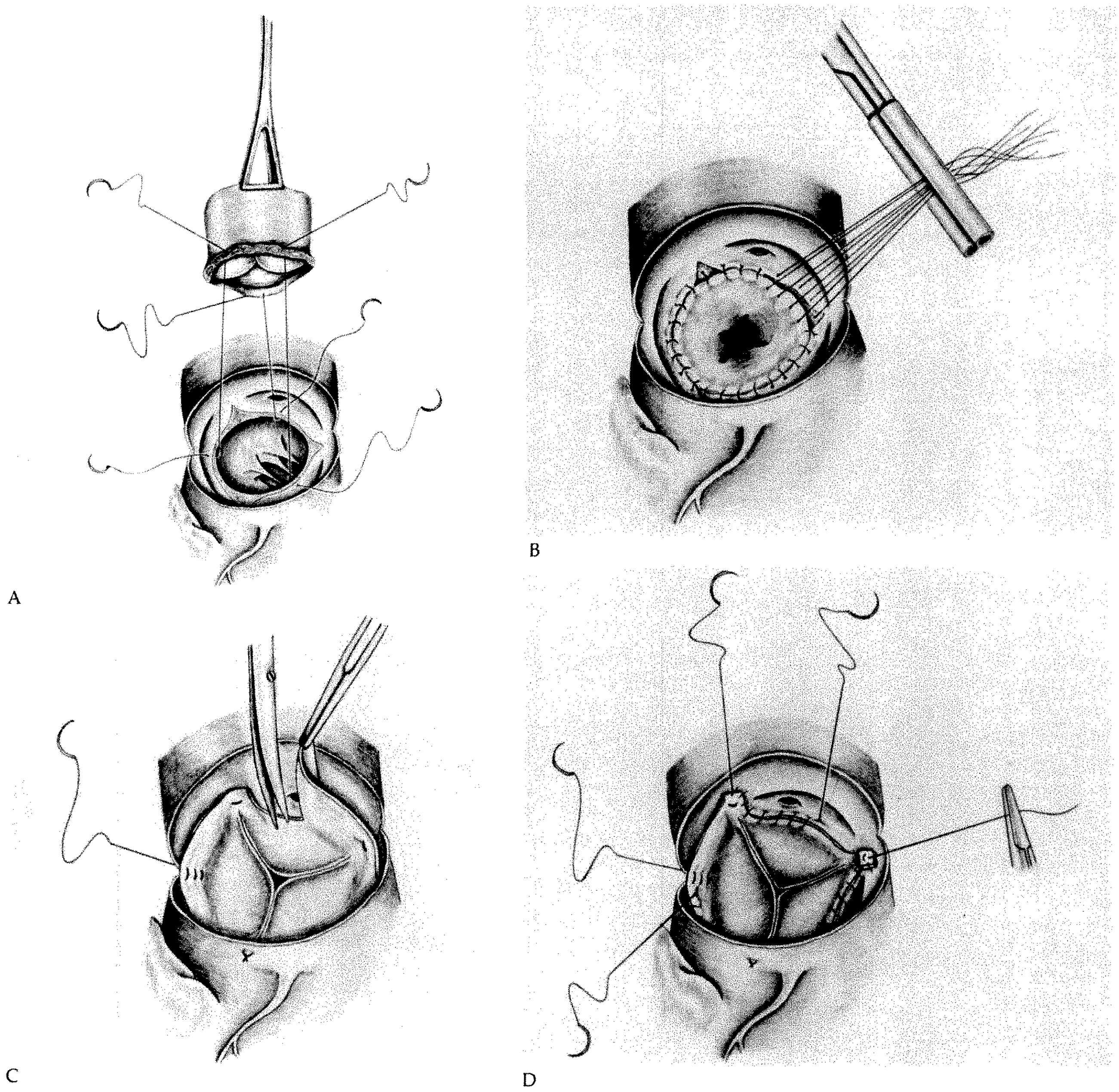

Fig 2. (A) The autograft is positioned in the aortic annulus by sutures placed at the midpoint of each sinus. (B) After placement of the proximal suture line the valve is seated and invaginated to allow for tying the sutures. (C) After the commissures are appropriately suspended, the autograft is trimmed below the coronary ostia. Closure of the aortotomy incorporates the wall of the autograft to obliterate dead space behind the noncoronary sinus. (D) The suture line is completed using a separate running polypropylene suture for each sinus.

All five perioperative deaths (5/39, 12.8% mortality) occurred in the subset undergoing left ventricular outflow tract reconstruction as a root replacement. However, several of these patients had more complicated outflow tract disease requiring root replacement. One patient had a large pseudoaneurysm at the site of a Dacron conduit used to replace the ascending aorta. Another patient had endocarditis, multiple subannular abscesses, and unrecognized coronary artery disease at autopsy. All 20 patients undergoing the cylinder (intraaortic) replacement of the aortic valve survived. One late death occurred 7 months postoperatively due to progression of coronary artery disease in a patient after aortic homografting. There was no obvious trend in morbidity or mortality based solely on age. Mortality for autografts and homografts are shown with respect to age in Fig 4.

In 1 patient, serious aortic insufficiency developed after pulmonary autografting. This autograft was revised using an aortic homograft (root replacement). This patient's autograft had been inserted using the technique of Barratt-Boyes for "freehand" aortic homografts, which was used in the first three autografts before we adopted the cylinder technique of Donald Ross. Other complications have included a major perioperative stroke in 1 patient with resultant severe neurological defect, complete heart block requiring pacemaker insertion in 2 patients, and

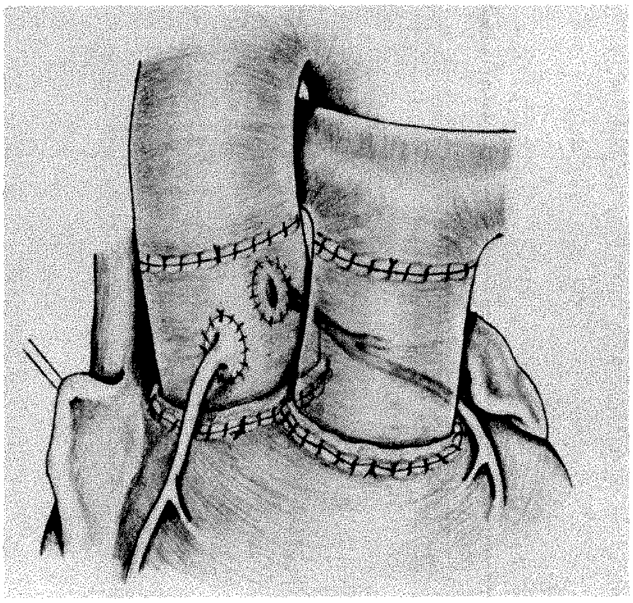

Fig 3. Root replacement with reimplantation of both coronary arteries and reconstruction of the right ventricular outflow tract with a cryopreserved pulmonary homograft.

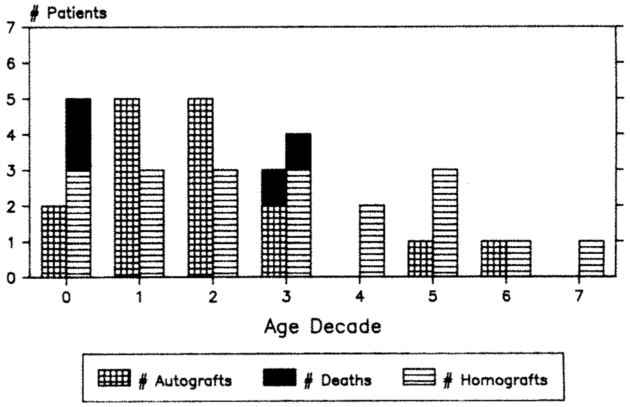

Fig 4. Mortality per decade with respect to autografts and homografts.

reexploration for bleeding in 1 patient. We did not use anticoagulants or antiplatelet agents unless they were required for coexisting disease; nevertheless, in limited follow-up, no patients have suffered thromboembolic complications. There has been no endocarditis. Forty-nine of 51 survivors are in New York Heart Association class I. One patient has moderate aortic insufficiency and is in New York Heart Association class II, and 1 patient cannot be evaluated due to a severe neurological deficit (normal postoperative echocardiogram). Postoperative echocardiography has been performed in all 51 survivors. None has demonstrated an obstructive gradient across the aortic valve or left ventricular outflow tract. Neither has any patient had evidence of stenosis or insufficiency involving the right ventricular outflow tract. Forty-eight of these patients have no or minimal aortic insufficiency. Three patients have moderate aortic insufficiency by echocardiography, but 2 of them are asymptomatic and have no diastolic murmur. Two patients with moderate insufficiency on their initial postoperative echocardiogram had complete resolution on multiple repeat studies (up to 1 year). We have not observed any patient with increasing insufficiency, and the short-term tendency appears to be that of improvement.

Table 2. Postoperative Results

Variable	No. of Patients
Mortality and morbidity	
Perioperative death	5
Late death	1
Complete heart block	2
Reexploration for bleeding	1
Postoperative myocardial infarction	2
Stroke	1
Echocardiography	
No AI to trace AI	51
Moderate AI	3
Severe AI	1
Postoperative NYHA class	
I	50
II	1
III	1[a]

[a] Patient underwent revision with an aortic homograft and is currently in NYHA class I.

AI = aortic insufficiency; NYHA = New York Heart Association.

Comment

Successful reconstruction of the left ventricular outflow tract using homograft (allograft) valves has been well documented [3, 5, 7–9]. O'Brien and co-workers [3] have recently showed that cryopreserved allograft valves are superior to fresh allografts stored at 4°C; their improved longevity appears to be due to persistent viability of leaflet cellular structures. Furthermore, successful cryopreservation allows longer valve storage times and increases the utility of the valves.

The less commonly performed pulmonary autograft also has been shown to be very effective in the aortic position [4, 10–12]. Moreover, Matsuki and co-workers [9] contend that "the long-term performance of a pulmonary autograft inserted for aortic valve disease is superior to that of any other valve substitute and that the operation offers an almost ideal means of aortic valve replacement in appropriate patients."

Because a relatively large pediatric population at our institution has aortic valve disease, and because of a general dissatisfaction with the performance of mechanical and porcine valves in this group and the need for a long-term solution to the problem, in November 1985 we embarked on a plan to use allograft and autograft valves in appropriate patients. Provisions to procure cadaveric homografts were very successful [13]. In general, our current philosophy has been to use the pulmonary autograft in patients with a life expectancy greater than 20 to 30 years. We believe that the aortic homograft (cryopreserved) is the ideal conduit or valve for patients with a life expectancy of 10 to 20 years and that the porcine heterograft is the best valve for patients aged more than 60 years requiring an aortic valve operation, which means that patients aged less than 40 years of age usually receive a pulmonary autograft. There have been notable exceptions, and we have successfully placed a pulmonary autograft in a healthy 62-year-old patient.

Our initial experience (beginning November 1985) was with the cryopreserved aortic homograft. Pleased with this undertaking, we performed our first pulmonary autograft in August 1986. We have been able to accomplish this rather formidable procedure with a mortality rate of 8.6%, comparable with the 8.3% obtained with homograft replacement of the left ventricular outflow tract. The higher mortality in patients undergoing aortic root replacement (12.8% versus 0%) appears to reflect a more serious disease process combined with a higher incidence of major hemorrhage.

Of the 51 survivors in our series, 49 (96%) are now in excellent health, are asymptomatic with respect to their heart disease, and are not restricted due to chronic anticoagulation. We have not observed a single thromboembolic event, and no endocarditis has occurred. Theoretically, these valves may represent a "final" operation for many of those patients, particularly those receiving pulmonary autografts [12, 13]. We agree with other investigators [3,12] that in appropriate patients allograft and autograft valves are the ideal choice for reconstruction of the left ventricular outflow tract.

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Cardiac Retransplantation in the Cyclosporine Era

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Between December 1980, when immunosuppression with cyclosporine was introduced, and May 1988, 288 patients underwent primary transplantation for end-stage cardiac disease (group TX). Fourteen patients underwent retransplantation for accelerated graft atherosclerosis (group RTXAGA), and 9 underwent retransplantation for intractable acute allograft rejection (group RTXREJ). Cumulative patient follow-up was 724 patient-years (range, 1 month to 7.5 years; mean, 2.3 years). Within the first 3 postoperative months, no differences were noted between groups for linearized rates of infection or rejection except between the rate of rejection for group TX (1.69 ± 0.09 events/100 patient-days) and group RTXAGA (0.94 ± 0.3 events/100 patient-days) ($p < 0.02$). No significant differences existed between groups for actuarial rates of remaining rejection-free or infection-free for more than 7.5 years. No significant differences in actuarial survival existed except between group TX (81% ± 2% at 1 year and 58% ± 4% at 5 years) and group RTXREJ (44% ± 17% at 1 year and 44% ± 0% at 5 years) ($p < 0.05$). We conclude that patients who undergo retransplantation for accelerated graft atherosclerosis experience a lower rate of early rejection and similar rates of infection and survival compared with patients who receive primary transplants. Cardiac retransplantation for rejection incurs rejection and infection at rates similar to those of primary procedures. However, patients who undergo retransplantation for rejection survive these complications significantly less often than do patients who receive primary transplants. This information should be considered when scarce donor hearts become available and retransplantation is contemplated.

(Ann Thorac Surg 1989;48:350–5)

Since the initial application of cardiac transplantation to the treatment of end-stage cardiac disease, many techniques have contributed to its ever-improving success, including refinements in surgical technique, improvement in donor and recipient evaluation, improvements in immune suppression, and treatment of acute allograft rejection [1–3]. Important among these innovations have been the introduction of cardiac retransplantation in 1975 and immunosuppressive therapy with cyclosporine in 1980. Clearly cardiac retransplantation has been shown to prolong recipient survival, but most reports have involved few patients [4] or examined the practice in the precyclosporine era [5]. To assess the early and late results of cardiac retransplantation at Stanford University Medical Center during the current era of immunosuppression with cyclosporine, a retrospective analysis was performed.

Patients and Methods

Between December 1980 and May 1988, 288 patients underwent primary transplantation for end-stage cardiac disease. Of these 288 patients, 138 (48%) underwent transplantation for the diagnosis of cardiomyopathy, 135 (47%) for coronary artery disease, and 15 (5%) for other indications, including congenital and valvular heart disease. Twenty-three patients underwent retransplantation for current or impending allograft failure for accelerated graft atherosclerosis (AGA) or for intractable acute graft rejection. Four patients received conventional immunosuppressive therapy consisting of azathioprine, corticosteroids, and antilymphocyte globulin after receiving their first allografts. All other patients in this study received cyclosporine as part of the immunosuppressive regimens after transplantation of the first and second allografts. Two patients who received a third allograft heart were excluded from the study. The patient population profiles are shown in Table 1.

Patients accepted for transplantation had terminal decompensation with severe functional disability and an expected survival measured in months. Candidates for retransplantation due to severe AGA (RTXAGA group, n = 14) were judged to be in a precarious clinical state from impending coronary occlusion demonstrated by coronary arteriography. Patients in the RTXAGA group were hemodynamically stable, with only 1 of 14 requiring intensive care monitoring and inotropic support. Candidates for retransplantation for acute allograft rejection (RTXREJ group, n = 9) were usually hemodynamically unstable, with 7 of 9 patients requiring intensive care nursing and inotropic support. One patient in the RTXREJ group was supported for 24 hours with a left ventricular assist system, and 2 others were treated with intraaortic balloon counterpulsation until donor hearts for retransplantation could be located. Absolute contraindications to transplantation and retransplantation included elevated pulmonary vascular resistance, active infection, positive donor-specific lymphocyte crossmatch, insulin-dependent diabetes mellitus, or irreversible renal, hepatic, or pulmonary

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Table 1. Population Profiles of Transplanted and Retransplanted Patient Groups

Variable	TX (n = 288)	RTXAGA (n = 14)	RTXREJ (n = 9)
Male sex	220 (76%)	14 (100%)	6 (67%)
Mean age (yr)	39	42	36
Ischemic time (min ± SE)	126 ± 57	107 ± 42	129 ± 66[a]

[a] Differences between groups lack significance.

RTXAGA = patients retransplanted for accelerated graft atherosclerosis; RTXREJ = patients retransplanted for intractable acute rejection; SE = standard error; TX = patients transplanted primarily.

dysfunction. Relative contraindications included advanced age and psychosocial instability. Selection of recipients and donors has been well described previously [2].

Donors were brain-dead individuals who suffered head trauma or cerebrovascular accidents. Donor hearts were harvested locally or distantly, and graft preservation was accomplished with topical hypothermia and pharmacological arrest. Orthotopic transplantation was performed by the technique described by Lower and Shumway [6].

Immunosuppression with cyclosporine was used for all patients. Several changing protocols have been used over the past 8 years. In general, the protocol changes were implemented to decrease the administered doses of cyclosporine and corticosteroids to avoid the complications of these agents. The most recent protocol change was made to utilize murine monoclonal antibody for rejection prophylaxis in the early postoperative period. The current protocol includes cyclosporine at a preoperative oral dose of 0 to 8 mg/kg followed by a daily oral dose administered to maintain a trough serum concentration of 100 to 150 ng/mL as measured by radioimmunoassay. Azathioprine is administered intravenously at 4 mg/kg preoperatively and is maintained at a dose of 2 mg/kg/day adjusted according to the white blood cell count. Methylprednisolone is administered intraoperatively (500 mg at the conclusion of cardiopulmonary bypass) and postoperatively (125 mg every eight hours for three doses). Prednisone is administered at a daily oral dose of 1 mg/kg and is gradually tapered over the ensuing 2 months to 0.2 mg/kg/day. OKT3 murine monoclonal antibody (5 mg) is administered intravenously daily postoperatively for 14 days.

Rejection was suspected on clinical grounds or detected on routine endomyocardial biopsy. Rejection graded as moderate or severe on biopsy [7] was treated initially with intravenous methylprednisolone (1 g daily for three days) or prednisone (100 mg orally for three days) followed by a 2-week tapering schedule. If rejection persisted after two courses of methylprednisolone therapy or was accompanied by hemodynamic changes, antithymocyte globulin or, more recently, murine monoclonal antibody was used. In one patient, actinomycin D was used successfully to reverse a prolonged rejection episode. Continuing rejection, as evidenced by endomyocardial biopsy despite these treatment regimens, was an indication for retransplantation.

Discharged patients underwent routine yearly cardiac catherization, endomyocardial biopsy, and coronary arteriography to assess the hemodynamic state and the presence and progression of AGA. Severe anatomical narrowing of graft coronary arteries was an indication for retransplantation.

For purposes of data analysis, patients were placed into three groups: primary transplantation (TX group, n = 288); retransplantation for development of severe accelerated graft atherosclerosis (RTXAGA group, n = 14); or retransplantation for intractable acute rejection (RTXREJ group, n = 9). Data examined included the linearized rates of rejection and infection for the first 3 postoperative months, the period of greatest risk for these complications. Linearized rates were compared using the unpaired *t* test. Actuarial rates of freedom from rejection, actuarial rates of freedom from infection (defined as requiring treatment or causing symptoms), and actuarial rates of survival were calculated for the 7.5-year period of the study. Cutler-Ederer calculations were used to derive Kaplan-Meier actuarial rates [8, 9] and the Gehan test was used for statistical analyses comparing actuarial curves [10]. Statistical significance was defined by a p value less than 0.05. Follow-up time for the TX group ranged between 1 month and 7.5 years (average, 2.4 years); the cumulative follow-up duration was 684 patient-years. For the RTXAGA group, follow-up time ranged from 1 month to 7.3 years (average, 2.0 years), and the cumulative follow-up was 28.1 patient-years. The RTXREJ group follow-up ranged from 1 month to 4.8 years (average, 1.4 years), and the cumulative follow-up duration for this group was 12.3 patient-years. Follow-up was complete for all patients through May 1988.

Results

Rejection

The linearized rate of rejection for the first 3 postoperative months was 1.69 ± 0.09 (± standard deviation) events/100 patient-days for the TX group. In comparison, the linearized rates of rejection for the same period for the RTXAGA and RTXREJ groups were 0.94 ± 0.3 and 2.09 ± 0.6 events/100 patient-days, respectively. The RTXAGA group experienced fewer rejection events in comparison with the TX group only ($p < 0.02$).

Actuarial freedom from rejection during the 7.5-year period was 14% ± 2% (± standard error) at 1 year and 4% ± 3% at 5 years for the TX group. Of the RTXAGA group, 27% ± 14% were free of rejection at 1 year, but all had experienced rejection by 3.6 years (Fig 1). In the RTXREJ group, all patients at risk had experienced rejection by 3 months (Fig 2). No statistical difference was noted when actuarial rates of freedom from rejection were compared between groups.

Infection

The linearized rates of infection for the first 3 postoperative months were 0.66 ± 0.05 (± standard deviation)

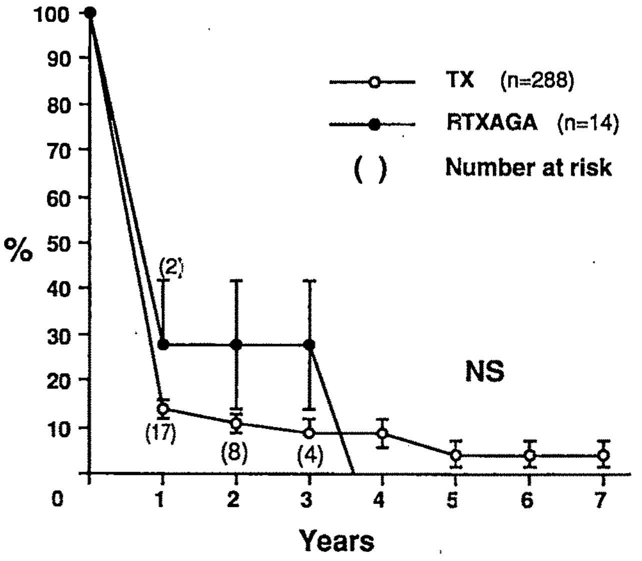

Fig 1. Actuarial freedom from rejection. Bars indicate ±standard error. (NS = not significant; RTXAGA = patients retransplanted for accelerated graft atherosclerosis; TX = patients transplanted primarily.)

events/100 patient-days for the TX group, 1.34 ± 0.37 events/100 patient-days for the RTXAGA group, and 1.29 ± 0.45 events/100 patient-days for the RTXREJ group. Differences were not statistically significant.

Actuarial freedom from infection during the 7.5-year study period was 23% ± 3% (± standard error) at 1 year and 12% ± 2% at 5 years for the TX group. Of the RTXAGA group, 33% ± 13% remained free of infection at years 1 and 5 (Fig 3). Thirty-three percent ± 18% of the RTXREJ group remained free of infection at years 1 and 5 (Fig 4). There were no statistical differences when actuarial rates of freedom from infection were compared between groups.

Survival

During the 7.5-year study period, actuarial survival of 81% ± 2% (± standard error) at 1 year and 58% ± 4% at 5 years was achieved for the TX group. Of the RTXAGA group, 85% ± 10% were alive at 1 year and 30% ± 22% at 5 years. There was no statistically significant difference between these curves (Fig 5). Actuarial survival of 44% ± 17% at 1 year and 44% ± 0% at 5 years was achieved in the RTXREJ group. The actuarial survival of the RTXREJ group was significantly less than that achieved by the TX group ($p < 0.05$) (Fig 6).

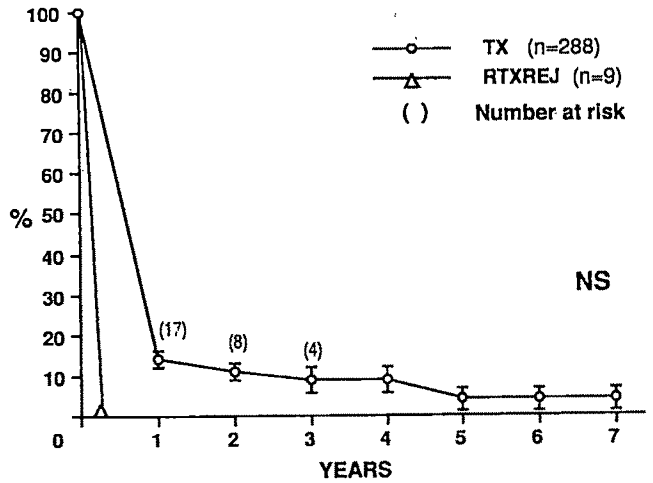

Fig 2. Actuarial freedom from rejection. Bars indicate ± standard error. (NS = not significant; RTXREJ = patients retransplanted for intractable acute rejection; TX = patients transplanted primarily.)

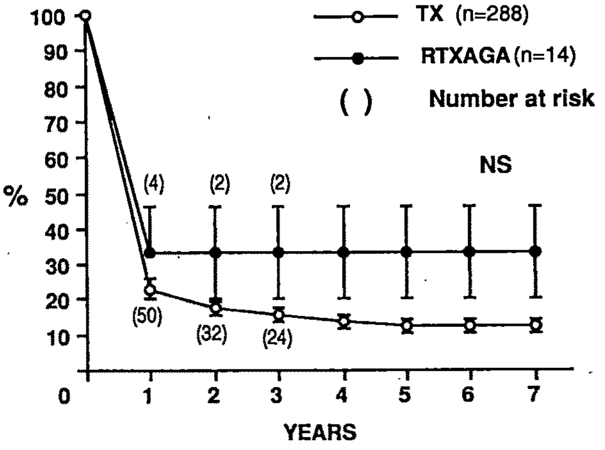

Fig 3. Actuarial freedom from infection. Bars indicate ± standard error. (NS = not significant; RTXAGA = patients retransplanted for accelerated graft atherosclerosis; TX = patients transplanted primarily.)

Cause of Death

Niney-three of 288 patients in the TX group have died; the causes of death are listed in Table 2. Five of 14 patients in group RTXAGA died, and 5 of 9 patients in group RTXREJ died. The causes of death were determined by clinical evaluation or by postmortem examination if available. The specific times and causes of individual patient deaths are listed in Table 3 for group RTXAGA and in Table 4 for group RTXREJ.

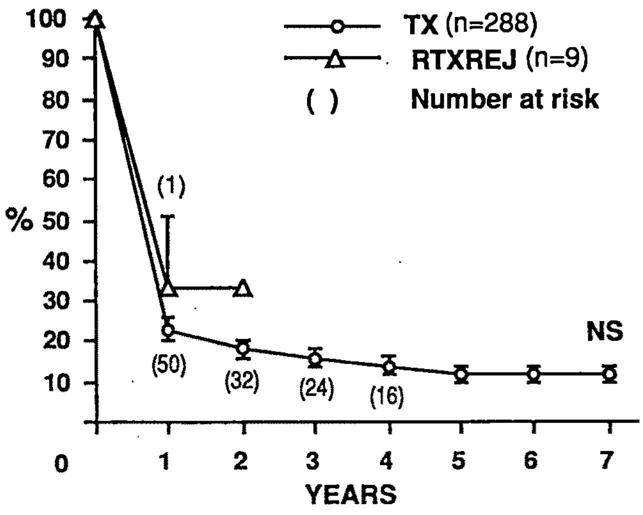

Fig 4. Actuarial freedom from infection. Bars indicate ± standard error. (NS = not significant; RTXREJ = patients retransplanted for intractable acute rejection; TX = patients transplanted primarily.)

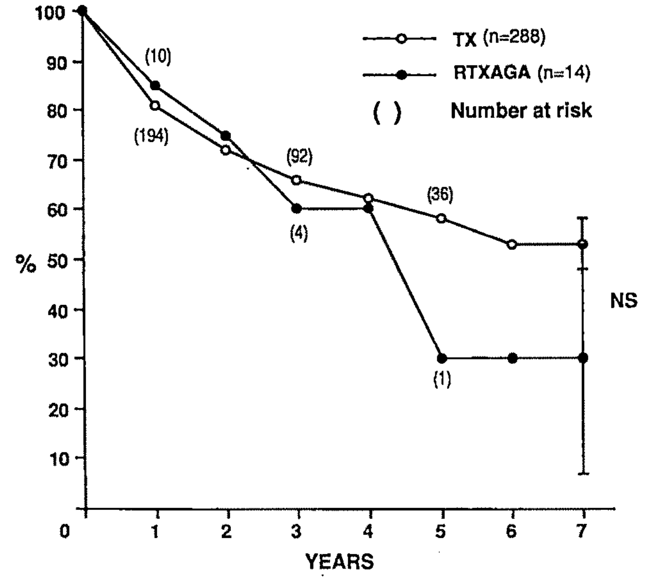

Fig 5. Actuarial survival. Bars indicate ± standard error. (NS = not significant; RTXAGA *= patients retransplanted for accelerated graft atherosclerosis;* TX *= patients transplanted primarily.)*

Functional Class

Of the 195 survivors in the TX group, 189 patients (97%) are in New York Heart Association (NYHA) functional class I and 6 are NYHA in class II. Eight of 9 (89%) survivors in the RTXAGA group are in NYHA class I, and 1 is in class II. All 4 survivors in the RTXREJ group are in NYHA class I.

Comment

Cardiac retransplantation for allograft failure, for a variety of causes including hemodynamic insufficiency, intractable arrhythmias, intractable acute rejection, and severe AGA, was introduced in 1975. The practice has clearly been shown to prolong survival, but overall numbers were small or results were reported during an earlier era when the "conventional" immunosuppressive regimen of azathioprine, corticosteroids, and antithymocyte globulin was used [4]. Watson and colleagues [5] reported the survival rate of second allograft hearts during the precyclosporine era to be approximately one half that for primary hearts, or 30% versus 60% at 1 year. With the small numbers of patients, inferences could not be drawn about results based on the specific indication for retransplantation. This review was undertaken to review current results of retransplantation using cyclosporine immunosuppression and to determine if these results were related to the indication for retransplantation.

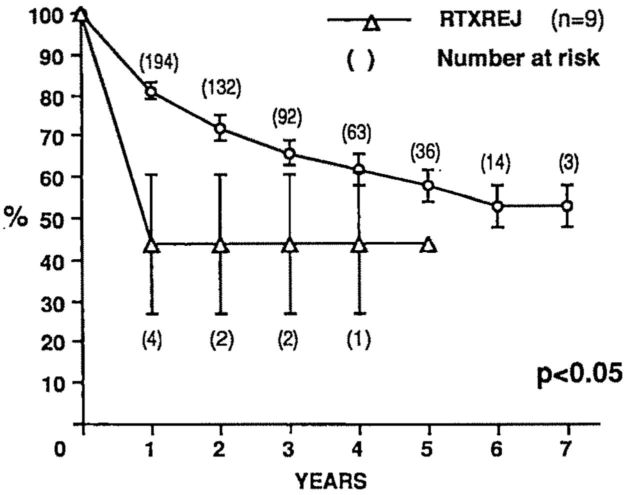

Fig 6. Actuarial survival. Bars indicate ± standard error. (RTXREJ *= patients retransplanted for intractable acute rejection;* TX *= patients transplanted primarily.)*

Table 2. Categorical Cause of Death for Patients Transplanted Primarily

Cause	No. of Patients
Infection	35
Rejection	15
AGA	14
Nonspecific graft failure	6
Lymphoid malignancy	5
Nonlymphoid cancer	5
Other	13

AGA = accelerated graft atherosclerosis; Other = pulmonary hypertension, cerebrovascular disease, pulmonary embolus, or unknown cause.

The advent of cyclosporine in 1980 has generally been associated with improvement in 1-year survival from approximately 50% to 80% [11]. In the current series, the actuarial survival rates for the TX group was 81% at 1 year and 58% at 5 years. This was not significantly different than the actuarial survival of 85% at 1 year and 30% at 5 years for the RTXAGA group. Therefore, patients retransplanted for severe AGA probably can be expected to survive at rates similar to those of patients transplanted primarily. Patients transplanted for ongoing acute allograft rejection do not fare as well, however, as reflected in an actuarial survival rate of 44% at 1 and 5 years for the RTXREJ group. This poorer result is probably related to the precarious hemodynamic and immunologic state of these patients, as 8 of 9 required preoperative inotropic support or mechanical ventilation. Only 1 of the RTXAGA

Table 3. Time and Specific Cause of Death for Patients Retransplanted for Accelerated Graft Atherosclerosis

Patient	POD	Cause
1	47	CMV pneumonia
2	54	Fungal/bacterial pneumonia
3	430	AGA
4	848	AGA
5	1,569	Bowel perforation

AGA = accelerated graft atherosclerosis; CMV = cytomegalovirus; POD = postoperative day of death.

Table 4. Time and Specific Cause of Death for Patients Retransplanted for Intractable Acute Rejection

Patient	POD	Cause
6	1	Hyperacute rejection
7	1	Bacterial sepsis
8	76	CMV pneumonia
9	105	Rejection
10	210	Bacterial pneumonia

CMV = cytomegalovirus; POD = postoperative day of death.

group and approximately 10% of the TX group required such supportive measures. Thus, the indication for retransplantation is clearly associated with the resultant actuarial survival rates.

Up to 90% of rejection episodes, with cyclosporine-based immunosuppression, occur during the first 3 postoperative months [12]. Our data show that within this period the linearized rates of rejection for the TX (1.69 ± 0.09) and RTXREJ (2.09 ± 0.6) groups were similar. The RTXAGA group linearized rate of rejection was 0.94 ± 0.3, which is significantly less than that of the TX group only. Perhaps this difference results from the immunosuppression received by patients in the RTXAGA group before the second transplant procedure. The RTXREJ group, however, continued to experience rejection at a linearized rate similar to that of the TX group. Indeed, all RTXREJ patients at risk experienced rejection by 3 months after operation. This suggests that cardiac recipients undergoing retransplantation because of intractable acute rejection appear to remain at great risk for acute rejection of the second allograft, despite previous immunosuppressive therapy. Perhaps this indicates continuing immunological reactivity in this subset of patients. Indeed, 2 of the 5 deaths in the RTXREJ group were due to rejection, whereas none of the 5 deaths in the RTXAGA group were due to rejection. At present, murine monoclonal antibody is being used for early acute rejection prophylaxis, and although preliminary data indicate that this method may be efficacious in the TX group, the experience in the retransplantation group is too small (n = 3) to draw any meaningful conclusions.

The risk of infection as a consequence of immunosuppression is well known. Our data demonstrated no clear difference between the three groups with respect to actuarial rates of remaining infection-free for 7.5 years, or in the linearized rates of infection for the first 3 months, the period of greatest risk to the patient. During this period, 35 of 93 (37%) of the TX deaths were due to infection as compared with 2 of 5 deaths (40%) in the RTXAGA group and 3 of 5 deaths (60%) in the RTXREJ group.

The long-term survivors of each group fared well from the standpoint of cardiac function and quality of life. Although not specifically examined in this study, the satisfactory hemodynamic results after cardiac transplantation have been well documented [13]. All long-term survivors in the RTXREJ group and all but 1 of those in the RTXAGA group were in NYHA class I.

Development of AGA remains one of the continuing problems of cardiac transplantation. Before the use of cyclosporine, the incidence of AGA, measured by coronary arteriography, was 41.5% in 89 patients [14]. Since the introduction of cyclosporine, the incidence has been reported to be 33% in 132 patients. There is no statistically significant difference between these groups. Histologic evidence of the disease has been noted as early as 3 months after operation in patients dying of other causes [15]. Previous research by Gao and co-workers [14] attempted to identify risk factors for development of AGA. No statistical correlation was found between the original recipient diagnosis of ischemic heart disease or other end-stage heart disease, recipient age, number of HLA mismatches, number of episodes of acute rejection, or corticosteroid dosage, although there was correlation with respect to donor age and recipient plasma triglyceride level [14].

Most transplant institutions endeavor to control the diet and lipid profile of cardiac transplant recipients, and many patients receive antiplatelet agents, but these efforts have not had much impact. Theories of immune injury to endothelial cells have been proposed for the development of AGA, but a clear pathogenesis has not been identified. As a result, only cardiac retransplantation is an effective treatment for the advanced stage of this disease. The actuarial survival of these patients, which is similar to that of the primary transplant group, argues favorably for continued use of yearly postoperative coronary arteriography for all transplant recipients to detect AGA. In contrast to patients with intractable acute rejection, patients with severe AGA are usually hemodynamically stable when a second donor heart is located. We believe that retransplantation is clearly justified when severe AGA is diagnosed. If there is no contraindication to transplantation, the procedure is performed on an "elective" basis in a manner similar to any primary transplant procedure.

Cyclosporine has been associated with improved survival after cardiac transplantation, although long-term problems with hypertension and nephrotoxicity have been well documented [12,13]. Improved survival has been associated with reduced morbidity and mortality from infection. There has been a clear reduction in the severity of the rejection episodes [16]. Intractable rejection, however, will occur occasionally, and the clinician is then faced with a difficult situation. A patient who still meets the criteria for retransplantation can be expected to achieve an actuarial survival of 44% at 1 year, due to the high likelihood of rejection and the ever-present problems with infection. These patients are quite debilitated and usually require inotropic support and mechanical ventilation, and it is often difficult to determine when noncardiac organ system dysfunction has become irreversible. In this era of donor organ shortage, critical evaluation of the patient before transplantation and retransplantation is essential with respect to hemodynamic, pulmonary, renal, and liver function. Of 9 patients in our series who underwent retransplantation for intractable rejection, 4 long-term survivors enjoy a functional result equivalent to that of patients transplanted primarily. Therefore, retransplantation for acute allograft rejection remains, as in the precyclosporine era, a salvage maneuver, and the procedure should continue to be used for select patients who continue to meet strict recipient criteria. The expected outcome for these patients is not as good as that for patients who undergo primary transplantation, however, and this fact should also be considered when scarce donor hearts become available.

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Gastric Vascular Pedicle Patch Esophagoplasty for Stricture

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Three patients with Barrett's esophagus and strictures between the middle and distal thirds of the esophagus, of 5 to 26 years duration at the time of the plasty, were treated with an infradiaphragmatic Nissen fundoplication and gastric vascular pedicle patch esophagoplasty, based on the right gastroepiploic vessels. Follow-up for 2 patients has been 6 and 7 years; both patients are asymptomatic except for periodic mild dysphagia in 1. The third patient developed cancer after 1 symptom-free year, and had esophagectomy with colon interposition. The results of this operation justify its use in recalcitrant lower intrathoracic esophageal strictures that do not respond to antireflux operation or dilation.

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Strictures of the esophagus secondary to reflux esophagitis can occur at any level, especially when associated with Barrett's esophagus [1]. The best treatment for this process is the removal of the offending agent by an antireflux operation. In most patients the stenosis should disappear spontaneously or after several dilations [2, 3]. In those whose stenosis defies dilation, or persists because of transmural fibrosis, an esophagoplasty must be performed. Strictures near the gastroesophageal junction can be treated very effectively by a Thal-Nissen gastric serosal patch [4, 5]. If this technique were used for strictures at a higher level, an excessive amount of gastric fundus within the chest may produce serious complications or intolerance in some patients [6, 7]. To keep the fundic wrap beneath the diaphragm and avoid the occasional complication, we have treated effectively 3 patients with strictures between the middle and lower thirds of the esophagus by esophagoplasty with a patch developed from the gastric fundus and pedicled on the right gastroepiploic vessels.

Technique

Through a midline abdominal incision, the right gastroepiploic vessels are separated from the stomach on one side and the omentum on the other, extending from the pylorus to their extreme, where a 6-cm diameter patch of attached fundus is removed (Fig 1) and the stomach is closed transversely. If an antireflux operation has not been done previously, it is performed at this stage. The patch is labeled with long silk sutures for intrathoracic orientation, brought to the hiatus retrogastrically, and pushed into the mediastinum or right chest in a position that avoids twists of the pedicle. The abdominal incision is closed and the patient placed in lateral position, right-side up, and a thoracotomy is performed through the sixth interspace. The stricture is identified with a dilator inserted orally, and the esophagus is opened longitudinally at a right anterior position. Biopsy specimens are taken and the correctly oriented gastric patch is sutured to the defect with a single layer of nonabsorbable suture, avoiding kinks and twists of the pedicle (Fig 2). The incisions are then closed and the cavities drained appropriately.

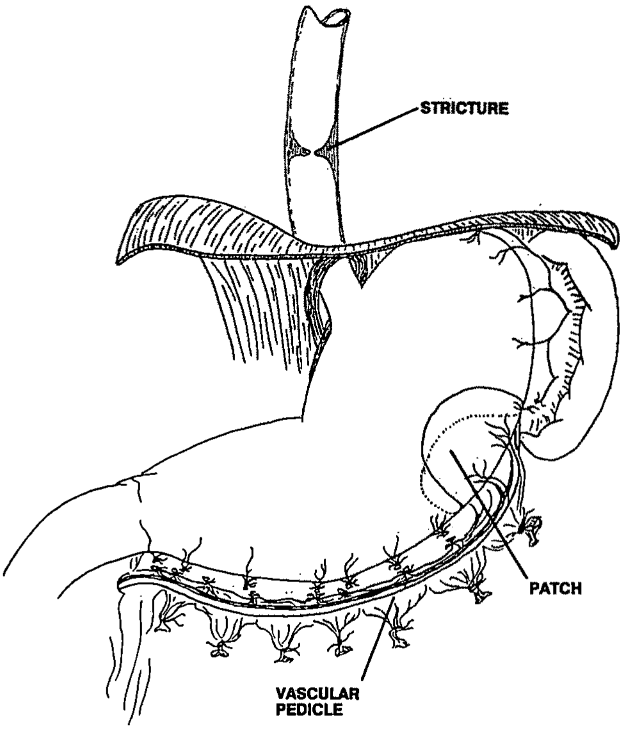

Fig 1. Intraabdominal development of the gastric patch pedicled on the right gastroepiploic vessels.

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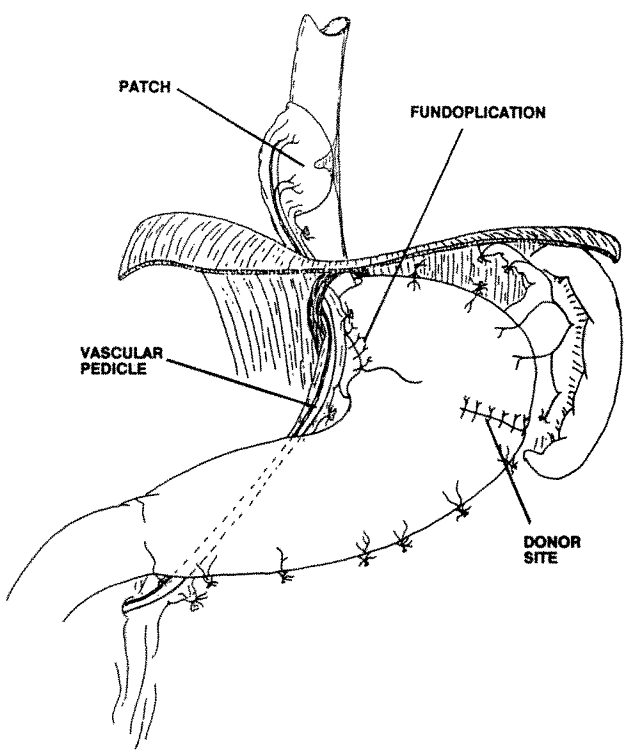

Fig 2. Intrathoracic gastric patch esophagoplasty with the right gastroepiploic pedicle following a retrogastric, transhiatal course.

Case Summaries

Patient 1

A 56-year-old woman had a perforation of the esophagus 6 years previously during the extraction of a foreign body and was treated by direct repair. Stricture persisted 10 cm from the gastroesophageal junction, needing periodic dilations, which became more frequent and more difficult. This was repaired with a gastric patch esophagoplasty pedicled on the right gastroepiploic vessels. Distal esophageal mucosa biopsy showed gastric mucosa. A Nissen fundoplication was done for reflux. Immediate postoperative Gastrografin (diatrizoate meglumine and sodium meglumine) swallow showed a small leak, but a posterior extrapleural drainage of the area yielded no accumulated fluid and she healed uneventfully. The patient has been followed 7 years and has remained asymptomatic.

Patient 2

A 7-year-old girl with dysphagia for 5 years, weighing only 18 kg, was found to have a stricture 8 cm from the gastroesophageal junction by roentgenograms. The stenotic area was treated with a gastric patch esophagoplasty pedicled on the right gastroepiploic vessels and reflux treated with a Nissen fundoplication. Distal esophageal biopsy showed gastric mucosa and the stricture showed transmural fibrosis. There were no postoperative complications, and the child has been followed 6 years with only one episode of choking on food which disappeared spontaneously.

Patient 3

A 57-year-old man was seen with a totally obstructed esophagus; he had undergone a direct esophagoplasty for stricture 25 years previously. At operation the stricture was found at 5 cm above the gastroesophageal junction and a Thal-Nissen fundic serosal wrap was selected as treatment. In spite of acceptable immediate postoperative contrast radiographic findings, the patient complained of intolerable bloating and postprandial substernal pain. By 3 months a stenosis was demonstrated at the same level (Fig 3A). At exploration the previous operation was taken down, stenosis was resolved with a gastric patch esophagoplasty pedicled on the right gastroepiploic vessels, and a fundoplication was constructed at an infradiaphragmatic position (Fig 3B). Biopsy of the stricture showed transmural fibrosis and the distal esophagus showed gastric mucosa with atypia. At 1-year follow-up the patient was asymptomatic, but a random biopsy per esophagoscope surprisingly showed invasive squamous cell carcinoma. The patient was treated by transhiatal esophagectomy and colon interposition. In the specimen the

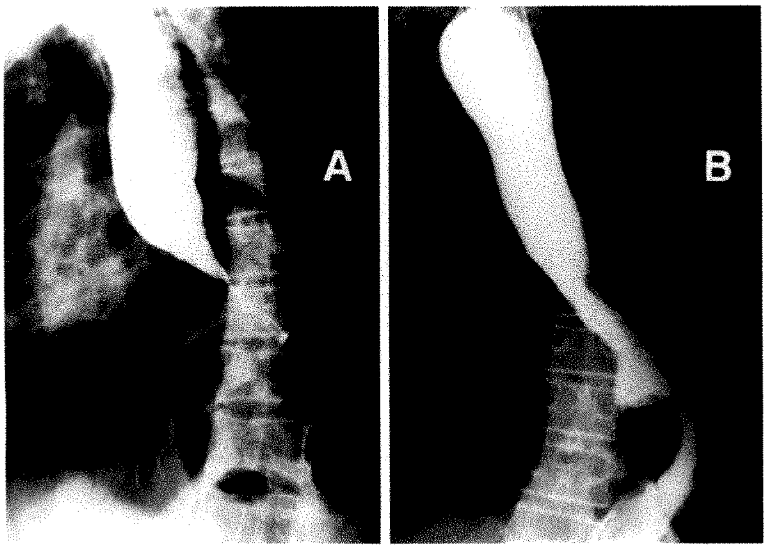

Fig 3. (A) Intrathoracic stricture; (B) stricture resolved with a gastric vascular pedicle patch esophagoplasty.

remains of the cancer were not found, and the patient is alive and well at 1 year.

Comment

An intrathoracic Nissen fundoplication prevents gastroesophageal reflux very effectively, but it is not tolerated by some patients, producing an exaggerated "gastric bloat" syndrome. There are no data at present to show that this occurs more frequently when the fundoplication is within the chest; however, its severity in this position is dramatic and the patient expresses his or her discomfort emphatically. Bearing no relation to the subjective experience, ulcers of the intrathoracic fundus have been observed and perforations described. Whether this is due to technical details, such as the size of the diaphragmatic opening or redundancy of fundus within the chest, is highly debatable. We have encountered a considerable number of these problems, and have been forced to revise an initial prejudice in favor of the intrathoracic Nissen fundoplication. Due to the unpredictability of these complications, we prefer to keep the fundoplication within the abdomen whenever possible until a clearer definition and solution to the problem is described.

An intestinal patch on a vascular pedicle is a good way to get a portion of bowel wall into the chest to construct an esophagoplasty without tension, avoiding restenosis and the need for an intrathoracic gastric fundus. Pedicled gastric patch esophagoplasty has been described based on either the right or left gastroepiploic vessels in the dog [8], and on the left gastroepiploic vessels in the human [9]. Usually, our patients do not have identifiable connections between the right and left gastroepiploic vessels at the greater curvature, and the left gastroepiploic turns out to be a longer short gastric. Due to their length, the right gastroepiploic vessels were selected to serve as the pedicle for the gastric patch, and they have been shown to cover the distal 10 cm of esophagus comfortably. Whether the patch carries antral or fundic mucosa seems to be unimportant, as evidenced by the benign follow-up of our patients with respect to recurrent esophagitis, stenosis, or symptoms.

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Amiodarone-Induced Complications After Cardiac Operation for Obstructive Hypertrophic Cardiomyopathy

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The occurrence of unanticipated and seemingly unexplicable major complications of hepatic, pulmonary, and cardiac dysfunction after palliative operation for obstructive hypertrophic cardiomyopathy prompted a review of 71 sequential patients. Fifty-five patients had been treated preoperatively with β-blockers, calcium-channel inhibitors, or both, and 16 had received amiodarone for six to 566 days (mean time, 210 days) at total doses ranging from 8 to 175 g (mean dose, 82 g) and had drug-free intervals prior to operation of zero to 457 days (mean time, 91 days). Comparisons were made between the two treatment groups and between those with and without major complications within the amiodarone-treated group. Preoperative cardiac studies, sex, age, functional class, and type of operation were not related to outcome for the entire patient cohort. In amiodarone-treated patients, the major findings were as follows: a 50% incidence of hepatic dysfunction with a tenfold increase in concentrations of serum glutamic-oxaloacetic transaminase and serum glutamic-pyruvic transaminase; a 25% incidence of pulmonary dysfunction necessitating a fourfold increase in the number of days of ventilator support; and a 19% incidence of low cardiac output syndrome with two deaths. Only 44% of the amiodarone-treated group had no serious complications. The incidence of major complications of the liver, lungs, and heart was 2%, 0%, and 2%, respectively, in patients not treated with amiodarone. Abnormal preoperative pulmonary function studies were predictive of prolonged postoperative ventilatory support. Discontinuation of amiodarone for several months prior to operation appeared to reduce the incidence of major complications. The necessary drug-free interval required preoperatively could not be determined from this retrospective experience. The recommendations resulting from this analysis are as follows: amiodarone should be discontinued and the operation delayed for as long an interval as possible; any abnormality in liver or pulmonary function studies should delay the procedure; and patients and referring physicians should be informed of the probability of increased complications, especially if the treatment regimen included more than 100 g of amiodarone for 300 days or more. It is concluded that caution must be used when patients who have been treated with amiodarone are being considered for surgical palliation of obstructive hypertrophic cardiomyopathy.

(Ann Thorac Surg 1989;48:359–64)

Amiodarone, an iodinated benzofuran derivative [2-butyl-3-(3,5,diiodo-4-β-diethylaminoethoxybenzoyl)-benzofuran hydrochloride] was introduced in Europe in 1967 as an antianginal agent [1]. Structurally similar to thyroxin, it has since found widespread use in Europe, South America, and eventually in the United States as an antiarrhythmic agent effective against both ventricular and supraventricular arrhythmias [2–7]. In 1986, it was approved for use in the United States by the Food and Drug Administration for treatment of documented life-threatening recurrent arrhythmias, recurrent ventricular fibrillation, and recurrent hemodynamically unstable ventricular tachycardia [8].

Although amiodarone was originally thought to have very low toxicity [2, 3], numerous reports have listed an alarming number of serious side effects including pulmonary fibrosis [4–7, 9–13], hepatic dysfunction [4–7, 11], proarrhythmic effects [2, 4], and worsening of cardiac failure [3, 5, 7]. Despite these reports of its toxicity, little is known about the effects of amiodarone on patients with hypertrophic cardiomyopathy who undergo a cardiac operation after preoperative treatment with this agent. This study was undertaken because several major unexplainable complications occurred in patients who underwent operative intervention to relieve obstruction of hypertrophic cardiomyopathy after they had been treated with amiodarone.

Material and Methods

This report is the result of a retrospective review of 71 patients operated on at the Surgery Branch, National Heart, Lung, and Blood Institute, during the interval April 1, 1984, to September 1, 1986, for symptoms of obstructive hypertrophic cardiomyopathy. Each patient was referred for operation by the Cardiology Branch after having failed maximal medical therapy and remaining in

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Table 1. Summary of Data for Amiodarone-Treated Group

Patient No.	Protocol	Treatment Time (days)	Total Dose (g)	Average Dose (g/day)	Drug-Free Time (days)	Cross-Clamp Time (min)	Operation	Complication
1	Arrhythmia	303	175	0.578	457	118	MVR	Hepatic + pulmonary + LCOS
2	Symptoms	81	66	0.815	42	42	LVMM	None
3	Symptoms	100	48	0.480	3	76	LVMM	Hepatic
4	Symptoms	175	82	0.469	46	37	LVMM	Hepatic + severe photosensitivity
5	Symptoms	55	40	0.727	47	115	MVR	Pulmonary
6	Arrhythmia	566	128	0.226	0	49	LVMM	Hepatic + pulmonary
7	Symptoms + arrhythmia	41	35	0.854	228	46	LVMM	None
8	Symptoms	314	141	0.449	96	48	MVR	Hepatic + LCOS; died
9	Symptoms	100	60	0.600	191	61	LVMM	None
10	Arrhythmia	262	50	0.191	0	66	MVR	None
11	Symptoms	170	78	0.454	39	61	MVR	Hepatic
12	Arrhythmia	72	36	0.500	37	111	MVR	Photosensitivity + alopecia
13	Arrhythmia	396	168	0.424	17	60	MVR	Hepatic + pulmonary + severe alopecia
14	Arrhythmia	6	8	1.333	22	62	MVR	None
15	Arrhythmia	534	107	0.200	0	170	LVMM + RVOT resection	Hepatic + LCOS; died
16	Arrhythmia	182	92	0.505	234	46	LVMM	None

LCOS = low cardiac output syndrome; LVMM = left ventricular septal myotomy-myomectomy; MVR = mitral valve replacement; RVOT = right ventricular outflow tract.

New York Heart Association functional class III or IV. Sixteen patients had been treated preoperatively with amiodarone in varying doses and for varying intervals. Data were collected from reviews of the hospital chart, interviews with the patient or the referring physician or both, and review of the drug trial data. The 16 amiodarone-treated patients were compared with 55 patients with obstructive hypertrophic cardiomyopathy who were operated on during the same interval but did not receive amiodarone.

Patient Group Characteristics

The amiodarone-treated patients and the nonamiodarone-treated patients were similar in regard to age (43 ± 4 years versus 49 ± 2 years, respectively) and sex (44% male versus 45% male, respectively). They did not differ significantly in terms of the following: preoperative liver function tests (serum glutamic-oxaloacetic transaminase [SGOT], 20 ± 2 mIU versus 19 ± 2 mIU, and serum glutamic-pyruvic transaminase [SGPT], 28 ± 3 mIU versus 24 ± 3 mIU), pulmonary function tests (forced expiratory volume in 1 second, 83% ± 5% of predicted versus 88% ± 2% of predicted; forced vital capacity, 82% ± 5% of predicted versus 81% ± 2% of predicted; forced expiratory volume in 1 second to forced vital capacity ratio, 100% ± 2% of predicted versus 101% ± 2% of predicted; and pulmonary diffusing capacity of carbon monoxide, 74% ± 6% of predicted versus 75% ± 5% of predicted), or pulmonary artery pressures (systolic, 35 ± 14 mm Hg versus 32 ± 10 mm Hg; diastolic, 15 ± 8 mm Hg versus 14 ± 6 mm Hg; wedge, 13 ± 4 mm Hg versus 18 ± 6 mm Hg; and left ventricular end-diastolic, 16 ± 6 mm Hg versus 21 ± 0 mm Hg). In addition, there was no significant difference in preoperative ejection fraction (75% ± 10% versus 76% ± 12%).

All patients in the amiodarone-treated group had a diagnosis of obstructive hypertrophic cardiomyopathy with hemodynamically significant left ventricular outflow tract obstruction (rest or provoked gradients > 50 mm Hg). Eight patients were prescribed amiodarone because of preoperative arrhythmias refractory to standard medical therapy: supraventricular tachycardia (3), atrial fibrillation (3), and ventricular tachycardia (2) (Table 1). The 8 other patients were participants in a clinical trial evaluating the efficacy of amiodarone in relieving symptoms of obstructive hypertrophic cardiomyopathy.

The total number of days of amiodarone treatment ranged from six to 566 with a mean of 210 days (see Table 1). The total dose ingested ranged from 8 to 175 g with a mean of 82 g. The length of time from discontinuation of the drug to operation ranged from zero to 457 days with a mean of 91 days. The average dose ranged from 191 to 1,333 mg with a mean of 550 mg.

Operations performed were similar in the amiodarone-treated and nonamiodarone-treated groups: mitral valve replacement, 50% versus 45%, respectively, and left ventricular septal myotomy-myomectomy, 50% versus 55%, respectively. Average cross-clamp time was similar in both groups, 74 ± 10 minutes versus 73 ± 5 minutes, as was bypass time, 123 ± 14 minutes versus 118 ± 6 minutes. Two (13%) of the 16 amiodarone-treated patients and 1 (2%) of the 55 nonamiodarone-treated patients required an intraaortic balloon pump to be weaned from cardiopulmonary bypass. Myocardial protection methods, anesthesia techniques, preinduction and induction medications, and maintenance drugs were similar in both groups.

Statistical Analysis

Comparisons were made between the amiodarone-treated and nonamiodarone-treated groups and between those patients in the amiodarone-treated group who did not have complications versus those who did. The comparisons were performed using contingency table analyses and the Wilcoxon test.

Results

Complications

A summary of the complications encountered in both groups is shown in Table 2. Six (38%) of the patients treated with amiodarone had no complications. One had mild skin problems of photosensitivity and alopecia. Nine patients (56%) had major complications involving substantial hepatic, pulmonary, and cardiac dysfunction. Two of these patients died. The incidence of complications was significantly higher in the amiodarone-treated group compared with the nontreated group ($p < 0.05$).

Complete liver function tests were performed daily in all patients, though Table 3 provides the maximal values for only SGOT and SGPT. The incidence of hepatic dysfunction was 50% in the amiodarone-treated group and 2% in the other group. For all 16 patients in the former group, the mean maximal values of SGOT and SGPT were about ten times those in the latter group. Within the amiodarone-treated group, the mean values for patients who did not exhibit hepatic dysfunction versus those of patients who did were 53 and 1,939 mIU/dL, respectively, for SGOT and 34 and 1,325 mIU/dL, respectively, for SGPT.

Table 2. Postoperative Complications in Both Groups[a]

Complication	Amiodarone Treatment (n = 16)	No Amiodarone Treatment (n = 55)
Photosensitivity, alopecia (mild)	1	0
Hepatic	5	1
Hepatic + pulmonary	2	0
Pulmonary	4	0
LCOS	3	1
LCOS + hepatic	2	0
LCOS + hepatic + pulmonary	1	0
Total	10 (62.5)[b]	2 (4)
None	6 (37.5)	53 (96)
Death	2 (12.5)	0 (0)

[a] Numbers in parentheses are percentages. [b] Nine patients had one or more major hepatic, pulmonary, or cardiac complications; only 1 patient sustained just one major complication, a pulmonary complication.

LCOS = low cardiac output syndrome.

Table 3. Postoperative Data for Both Groups[a]

Variable	No Amiodarone Treatment (n = 55)	Amiodarone Treatment (n = 16)
Hepatic dysfunction		
SGOT (mIU/dL)[b]	95 ± 10; 3–132	950 ± 659; 37–10,700
SGPT (mIU/dL)[b]	75 ± 12; 5–183	782 ± 385; 14–6,120
Patients with severe dysfunction	1/55 (2)	8/16 (50)
Pulmonary dysfunction		
Ventilator (days)	0.8	4.3; 0.8–35
Moderate	0	1
Adult respiratory distress syndrome	0	3
Total	0 (0)	4 (25)
Low cardiac output syndrome		
Moderate (no IABP; drug responsive)	1	1
Severe (IABP; not responsive to inotropic drugs)	0	2
Total	1 (2)	3 (19)
Deaths	0	2 (12.5)

[a] Numbers in parentheses are percentages. [b] Data are shown as the mean ± the standard error of the mean; the range follows.

IABP = intraaortic balloon pump; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

Pulmonary dysfunction occurred in 25% of the amiodarone-treated group and necessitated 3, 7, 14, and 35 days of ventilatory support. No patient in the nonamiodarone-treated group required more than 24 hours of support.

Low cardiac output syndrome (LCOS), defined as a cardiac index of less than 2.0 L/min/m^2 and evidence of poor organ perfusion, occurred in 3 patients in the amiodarone-treated group. One of these patients also had hepatic and pulmonary dysfunction, which abated concomitantly in response to inotropic agents. The 2 patients with severe LCOS had gross hepatic dysfunction as well, and were unresponsive to inotropic drugs and intraaortic balloon treatment. These 2 patients died. Only 1 patient in the nonamiodarone-treated group sustained LCOS, and required substantial quantities of inotropic agents for a short time (less than 48 hours).

Relationship of Complications to Four Variables in Amiodarone-Treated Group

PREOPERATIVE DATA. Preoperative liver function test results did not predict which patients would or would not have major increases in serum enzyme concentrations in the immediate postoperative interval. The 7 patients without major dysfunction had mean values of 18.4 and 27.4 mIU/dL for SGOT and SGPT, respectively. The 5 patients with hepatic dysfunction, with or without pulmonary complications, had values of 19.2 and 28.4 mIU/dL for SGOT and SGPT, respectively. The one exception was the single patient in whom amiodarone-induced hepatitis developed preoperatively. She was operated on 39 days after discontinuation of amiodarone. At the time of operation, the liver function test results had returned to normal. Substantial hepatic dysfunction with maximal values of 1,225 and 1,835 mIU/dL for SGOT and SGPT, respectively, developed postoperatively.

Preoperative pulmonary function studies, on the other hand, were predictive of the development of complications. The mean values for forced expiratory volume in 1 second, forced vital capacity, and diffusing capacity of carbon monoxide for the 4 patients with postoperative pulmonary dysfunction versus the 9 without this complication who were tested were 71% versus 89%, 68% versus 87%, and 55% versus 83%, respectively. The presence of pulmonary hypertension preoperatively was not related, as 2 of the 3 patients with pulmonary hypertension had no pulmonary complications. The occurrence of amiodarone-induced pulmonary fibrosis preoperatively also seemed to predispose to severe pulmonary dysfunction postoperatively, as was seen in 1 patient despite normal pulmonary function test results.

The development of LCOS was not related to pulmonary hypertension or preoperative cardiac function. None of the 3 patients with this complication had elevated pulmonary artery pressures. All 3 had ejection fractions greater than 76% as measured by radionuclide angiography. The left ventricular end-diastolic pressures were not different from those in patients without the complication or those in the nonamiodarone-treated group.

Two patients with LCOS who subsequently died had cross-clamp intervals of 48 and 170 minutes, and the 1 patient with LCOS who survived had a cross-clamp interval of 118 minutes.

TOTAL DOSE. The 7 patients without major complications had a mean dose of 49.6 g. The 4 patients with hepatic dysfunction only or pulmonary dysfunction only had injected 62 g. The 5 patients with two or more complications had a mean total dose of 143.8 g with a range of 107 to 175 g. There was no significant difference between the mean dose of patients with a single major complication and that of patients without complications. However, patients who received more than 100 g were at high risk for two or more complications or death.

AVERAGE DAILY DOSE. The average daily dose ranged from 191 to 1,333 mg. The mean value for those without complications was 685 mg and for those with complications, 445 mg. No relationship was found with respect to the incidence of complications or any other variable.

DRUG-FREE PREOPERATIVE INTERVAL. The 7 patients without major complications had preoperative drug-free intervals ranging from zero to 234 days with a mean interval of 108 days. In 4 of these patients, the drug-free interval was 42 days or less. The 9 patients with complications had intervals ranging from zero to 457 days. However, for 8 of the 9, the interval was zero to 96 days with a mean of 31 days. Three patients had no drug-free interval prior to operation; 2 of them had major complications and 1 died. For the patients without complications, the mean drug-free interval was 1.4 days longer than the mean treatment duration. In contrast, the 9 patients with complications had a mean treatment duration 106.5 days longer than the mean drug-free interval.

Comment

Amiodarone has a wide variety of pharmacological effects. They include decreasing coronary vascular resistance and increasing coronary blood flow [14, 15], decreasing peripheral vascular resistance [14–16], causing an atropine-resistant sinus bradycardia [14, 16–18], causing a noncompetitive blockade of both α- and β-adrenergic receptors [14, 16, 17, 19], and a noncompetitive inhibition of both the inotropic and the chronotropic response to glucagon [17]. DeBoer and colleagues [20] showed that amiodarone favorably influenced hemodynamic values and decreased infarct size in experimental myocardial infarction. Charlier and associates [14] demonstrated in dogs that amiodarone had major negative inotropic effects, work later confirmed by others [15, 21]. In addition, amiodarone possesses numerous electrophysiological effects, which make it attractive as an antiarrhythmic agent. It results in a marked prolongation of both atrial and ventricular action potentials [18] and a substantial increase in the effective refractory period of the atrium, ventricle, atrioventricular node, His-Purkinje system, and accessory pathways [2].

The pharmacokinetics and pharmacodynamics of amiodarone are not highly predictable [5–7]. The drug has a low bioavailability after oral ingestion [22] and has an extremely variable half-life ranging from 20 to 80 days [3, 6]. There is evidence to suggest that amiodarone possesses tissue-specific uptake and concentration [22] in addition to tissue-specific activity [19].

Amiodarone has been proven in numerous clinical series to be highly efficacious as an antiarrhythmic agent effective against both supraventricular and ventricular arrhythmias [2–7]. Although its safety record during a decade of use in Europe and South America was impressive [2, 3], it has not found a similarly low risk/benefit ratio in the United States [2–7, 9–13]. Many reasons have been postulated to explain the higher incidence and severity of complications seen in the United States, the most convincing of which is that higher doses were used [4, 5, 7, 11], particularly for patients with drug-refractory arrhythmias [4].

Amiodarone is now prescribed for patients who will eventually require a cardiac operation, although there have been few reports of its use in the surgical setting [16, 21, 23]. We are aware of two case reports of patients in whom LCOS developed [16, 21], two cases of atropine-resistant sinus bradycardia [16, 23], and one case of complete heart block [23], all thought to be secondary to amiodarone.

The most consistent finding in these reports is the development of LCOS, reported by Gallagher and associates [16] in 1981 and by MacKinnon and colleagues [21] in 1983. Both of these studies, however, dealt with patients who had severe coronary artery disease and underwent coronary artery bypass grafting and resection of a left ventricular aneurysm. This group of patients can be expected to have an increased incidence of LCOS postoperatively, which is related to the underlying cardiac disease, thus making it difficult to implicate the drug as a cause of LCOS. In the patient reported by Gallagher and co-workers [16], an inappropriately low systemic vascular resistance (600 dyne-sec/cm^5), which was refractory to α-adrenergic agonists, developed. In addition, Liberman and Teasdale [23], in 1985, reported that 6 of 12 patients who had a variety of cardiac operations and were treated preoperatively with amiodarone required an intraaortic balloon pump to be weaned from cardiopulmonary bypass. They also noted that in 2 patients, a state of "alpha-adrenergic blockage" leading to a low systemic vascular resistance developed, despite α-agonist therapy.

The findings in this report support the previous citations of LCOS and clinically significant α-adrenergic blockade associated with the use of amiodarone. Although no test was found that would seem to indicate which patient was going to experience either LCOS or α-adrenergic blockade postoperatively, the development of pulmonary dysfunction postoperatively might be predicted on the basis of preoperative data. First, the development of pulmonary fibrosis preoperatively may place the patient at a higher risk of pulmonary dysfunction postoperatively, regardless of the pulmonary function variables at the time of operation. Second, a fall in pulmonary function test results (particularly the pulmonary diffusing capacity of carbon monoxide) to a level less than 80% of predicted that does not rise higher than 80% on withdrawal of amiodarone may place the patient at increased risk of pulmonary dysfunction postoperatively. Third, the development of drug-induced hepatitis while on a regimen of amiodarone may place a patient at risk for hepatic dysfunction even if the pulmonary function test results have returned to normal preoperatively.

Two or more major complications in the same patient appeared to be dose related because those patients receiving more than 100 g of amiodarone preoperatively had the highest incidence and severity of complications. The development of pulmonary or hepatic dysfunction or LCOS does not appear to be related to the length of time from discontinuation of the drug to the time of operation except in a general way. However, the duration of the drug-free interval was related to the incidence of complications when it was shorter than the duration of drug administration. The 7 patients without major complications had longer drug-free intervals (mean interval, 108 days) than those with complications (mean interval, 31 days). In view of the extremely long and variable half-life of amiodarone, the appropriate drug-free interval required is unknown.

Low cardiac output syndrome developed in 3 of the 16 amiodarone-treated patients, 2 of whom died, and in only 1 of the 55 nonamiodarone-treated patients without any clear predictor to indicate this outcome. One of the patients who died had the longest cross-clamp time (170 minutes), but this did not differ significantly from the longest cross-clamp time in the nonamiodarone-treated group (154 minutes). In addition, the other patient who died had a cross-clamp time of 48 minutes. Thus, time of ischemia by itself was not a predictor of either LCOS or death. The possibility remains, however, that the combination of a long period of ischemia and a substantial intake of amiodarone preoperatively (>100 g) places the patient at a higher risk of LCOS, death, or both.

A number of factors may be responsible for the variability in the drug-free interval. It is known that amiodarone uptake is, in part, tissue specific [22]. It is highly lipophilic, and penetrates and binds to tissues with high lipid content. It has been proposed that amiodarone binds to intracellular phospholipids and prevents the breakdown of these phospholipids [12]. The accumulation of phospholipids may then be responsible for some of the findings of dose-related toxicity, particularly in organs such as the lung [9, 12].

We urge cardiac surgeons to exercise increased caution in considering operative palliation for patients treated with amiodarone, particularly if one or more of the following factors are present: there is clinical evidence of pulmonary or hepatic dysfunction preoperatively; there is a decline in pulmonary function studies (particularly the pulmonary diffusing capacity of carbon monoxide) to values less than 80% of predicted; after withdrawal of the drug, the pulmonary function test results fail to reach normal levels (greater than 80% of predicted); or the patient has taken more than 100 g of amiodarone (total preoperatively), has taken the drug for 300 days or more, or has not had a drug-free interval equal to or greater than the drug treatment interval.

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Viable Cryopreserved Aortic Homograft for Aortic Valve Endocarditis and Annular Abscesses

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Six consecutive patients with active aortic valve endocarditis, including 2 with extensive subannular aortic root abscess, were successfully treated with viable cryopreserved homograft aortic valve replacement. Two patients required extensive aortic root reconstruction with an appropriately trimmed aortic homograft to cover large abscess cavities. All patients showed resolution of infection with no perioperative mortality or clinically significant morbidity. Three patients had a minor degree of aortic insufficiency on postoperative echo-Doppler study. On follow-up at 6 to 48 months, all patients were in New York Heart Association functional class I. The resistance of the unstented homograft to infection makes it an attractive choice for patients requiring aortic valve replacement for active endocarditis. The results of surgical intervention in patients with extensive aortic root involvement may be further improved by the flexibility afforded by the homograft to be "custom-fit" to the abnormal aortic root and the ability to achieve secure valve fixation without use of prosthetic material.

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Since the first successful surgical treatment of acute infective endocarditis, several large series have been reported that confirm the efficacy and low reinfection rate using mechanical valves [1, 2], xenografts [3], and nonviable homografts [4]. However, when infection is extensive, secure prosthetic valve placement can be technically challenging, and the incidence of paravalvular leak and valve dehiscence is still high, especially when annular abscess is present with endocarditis.

Aortic valve homografts, which have been shown to be virtually free of thromboembolic complications [5], have become a more attractive choice for aortic valve replacement with a demonstration by O'Brien and colleagues [6] that cryopreserved valves with viable leaflet tissue are significantly more durable than nonviable homograft valves. Likewise, Matsuki and associates [5], who have more than 20 years of experience with aortic valve homografts, conclude that the good quality of life and median life expectancy make the homograft an excellent choice for aortic valve replacement. The analysis by O'Brien and colleagues [6] of the hazard function for endocarditis in patients without preoperative valve infection showed a lack of an early phase of risk, supporting the idea that the aortic valve homograft has a special resistance to the development of early prosthetic valve endocarditis. This suggests that use of the aortic valve homograft may further decrease the reinfection rate for patients with active endocarditis, leading some investigators to consider it the prosthesis of choice in these patients [7]. The device has the added advantage of not requiring fixation of a rigid prosthetic sewing ring in an infected annulus while providing the flexibility of using the adjacent aortic wall and mitral valve for repair of major aortic root defects. We present a series of 6 patients with active aortic valve endocarditis who were treated by aortic valve replacement with a cryopreserved human aortic homograft and describe the technique used in the 2 patients with extensive annular abscesses in whom the homograft tissue was used to reconstruct the aortic root.

Material and Methods

Six patients underwent aortic valve replacement with viable cryopreserved human aortic homografts for active aortic valve endocarditis at The University of Texas Medical Branch in Galveston between January 1986 and December 1987. The demographic characteristics and the important clinical characteristics are summarized in Table 1. There were 5 men and 1 woman aged 31 to 53 years. Three patients were intravenous drug abusers. Three of the 6 patients had systemic emboli. Two patients had active aortic root abscesses, and the other 4 had active vegetations and valve destruction usually with some minor involvement of the aortic annulus.

The operative technique is as follows. Cardiopulmonary bypass is instituted using a single venous cannula; the aorta is cross-clamped, and the myocardium is protected by cold oxygenated crystalloid cardioplegia with intermittent cardioplegic reinfusion. A transverse aortotomy is made high enough not to interfere with the most superior portion of the homograft suture line and is extended into the noncoronary sinus of Valsalva midway between the commissures. The extent of tissue destruction of the aortic valve is assessed and the diseased tissue is then excised, with care taken to debride infected purulent material from the annulus, aortic wall, and ventricular septum. The diameter of the aortic root at the level of

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Table 1. Demographic and Clinical Characteristics

Patient No.	Age (yr)	Sex	Drug Abuse or Possible Source of Infection	Organism	Preoperative Complication	Operative Findings	Operative Procedures and Date	Doppler Findings Before Discharge	Murmur for AI
1	53	F	Chronic indwelling intravenous catheter	*Staphylococcus epidermidis*	None	Destruction of the noncoronary cusp and vegetation extending to the mitral valve	AVR homograft (20 mm)	Aortic root, 3.7 cm; LV, 5.5/3.6 cm; FS; 35%; No AI	No
2	27	M	Drug addict	*Neisseria gonorrhoeae*	None	Ruptured noncoronary cusp	AVR homograft (23 mm)	Aortic root, 3.0 cm; LV, 6.0/3.6 cm; FS general hypokinesia; mild AI	No
3	31	M	. . .	Culture-negative *Chlamydia* by immunoglobulin titers	Recurrent systemic emboli	Destruction and vegetation of the right and noncoronary cusps, right coronary ostial occlusion	AVR homograft (20 mm), single vessel coronary artery bypass graft	Aortic root, 3.0 cm; LV, 5.5/3.6 cm; FS, 34%; mild AI	No
4	39	M	Drug addict with previous heterograft AVR	*Streptococcus viridans*	Systemic emboli, complete heart block	Destruction of the right and noncoronary cusps with large annular abscess	AVR homograft (26 mm), repair with homograft	Aortic root; 4.0 cm; LV, 5.9/3.3; FS, 44%, ?mild AI	No
5	33	M	Drug addict	*Streptococcus fecalis*	Systemic emboli	Destruction and vegetation of the right and noncoronary cusps	AVR homograft (24 mm)	Aortic root, 2.7 cm; LV, 6.7/5.8 cm; FS, 13%; mild AI	Diastolic grade 2/6 8 mo after operation
6	41	M	. . .	Diphtheroids	Complete heart block	Destruction of the right and noncoronary cusps with an abscess involving the annulus and membranous and muscular septum	AVR homograft (22 mm) with repair of defect using homograft (see Fig 1)	Aortic root, 2.5 cm; LV, 5.0/2.2 cm; FS, 55%; no AI	No

AI = aortic incompetence; AVR = aortic valve replacement; FS = left ventricular fractional shortening; LV = left ventricular dimensions.

the annulus is determined using prosthetic valve-sizing devices. When determining this dimension, one must consider that the homograft size should be chosen on the basis of the diameter that will be used to support the homograft valve leaflets, as the defects created by an annular abscess and its debridement may allow oversizing if the annular diameter alone is used. Because of the thickness of the trimmed aortic homograft, the valve size chosen for replacement must be 2 to 3 mm smaller than the measured aortic annulus because the homograft size is measured as its internal diameter.

The aortic homograft is thawed by the recommended technique and then trimmed after assessment of the best orientation and the amount of contiguous aortic wall and mitral anterior leaflet needed to repair any existing aortic root defect. If no such defect exists, the valve and valve orientation are trimmed as described by Kirklin and Barrett-Boyes [7]. We now prefer to use interrupted mattress sutures (3-0 braided synthetic sutures) for the subannular suture line and place these while the homograft is being thawed and trimmed. The recommendation to rotate the homograft valve 120 degrees, thus placing the thick septal muscle of the graft opposite the flat portion of the outflow tract above the mitral valve, is controversial. In the 2 patients with large annular abscesses, the homograft was rotated so that the anterior mitral leaflet could be best used to repair the subannular defect (Fig 1). In 1 patient in this series, a portion of this suture line was done with pledgetted mattress sutures placed in healthy uninvolved septal muscle because of the friability of the muscular septum bordering the abscess. The homograft aortic wall of the appropriate sinus(es) of Valsalva is retained when the homograft is initially trimmed and, after the subannular suture line is completed, is then fashioned to close the extension of the abscess into the aortic wall above the annulus accurately (see Fig 1). The three suture lines to form the aortic sinuses and secure the homograft aortic wall to the host aorta are sewn with continuous 4-0 monofilament polypropylene suture.

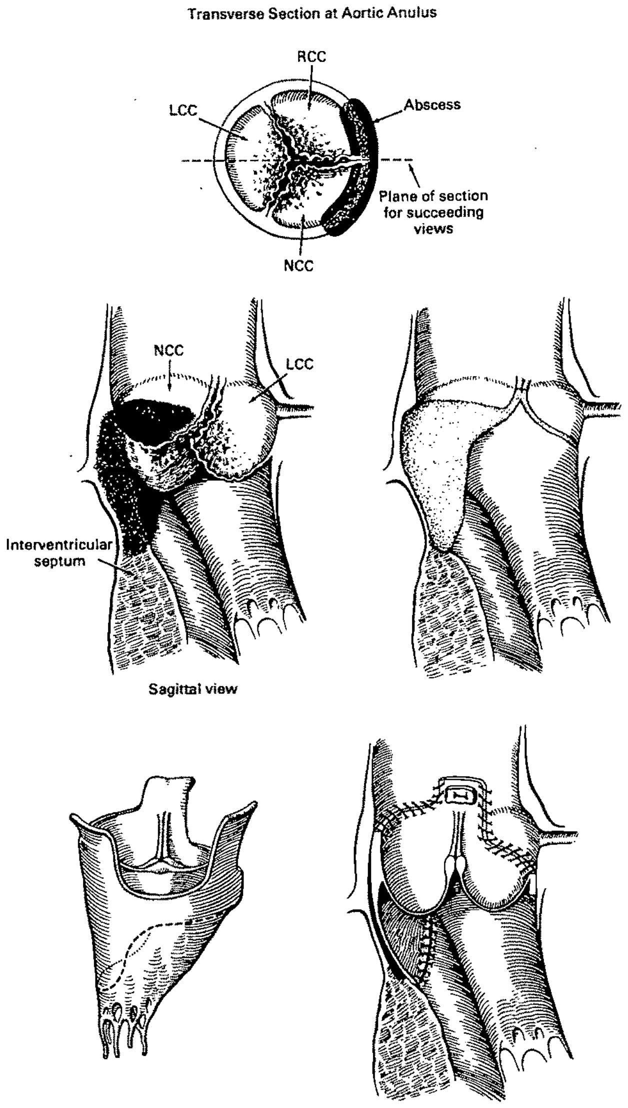
Transverse Section at Aortic Anulus
RCC
LCC
Abscess
Plane of section for succeeding views
NCC
NCC
LCC
Interventricular septum
Sagittal view

Fig 1. Custom-fit aortic homograft as replacement of aortic valve endocarditis with annular abscess. After debridement of the abscess, the homograft is rotated and trimmed so that the anterior mitral leaflet can be used to repair the subannular defect. (LCC = *left coronary cusp;* NCC = *noncoronary cusp;* RCC = *right coronary cusp.)*

Results

The clinical course of each patient is summarized in Table 1. All except the patient with *Chlamydia* endocarditis (patient 3) had positive blood cultures for the organism noted and were operated on during their initial antibiotic course for endocarditis. The length of antibiotic treatment for these 5 patients was: 3 days (patient 6), 3 days (patient 1), 12 days (patient 4), 31 days (patient 5), and 54 days (patient 2). In 5 of the 6 patients the intraoperative cultures showed no growth. In patient 1, coagulase-negative *Staphylococcus* grew from the aortic valve at the time of operation.

The aortic cross-clamp time ranged from 129 to 179 min (mean cross-clamp time, 145 min). Postoperative cardiac performance was good, but 1 patient required catecholamine support for 45 min. All patients were transferred out of the intensive care unit on the first postoperative day. There was no perioperative or late mortality, all patients showed marked functional hemodynamic improvement (Fig 2), and there were no cases of early homograft valve endocarditis. One of our patients (patient 1), who required repeated transfusion for aplastic anemia, experienced endocarditis and moderate aortic insufficiency 1.5 years after operation but has not required reoperation.

Complete heart block was present preoperatively in 1 patient (patient 6), who required a pacemaker. Postpericardiotomy syndrome was seen in 1 patient (patient 1) and spontaneous pneumothorax in 1 patient (patient 5). There have been no neurological or thromboembolic complications after operation.

Postoperative Doppler echocardiographic evaluation was performed shortly before hospital discharge; data are summarized in Table 1. Trivial aortic incompetence was detected in 2 patients (patients 2 and 3), and 1 patient (patient 5), who was asymptomatic, had mild to moderate

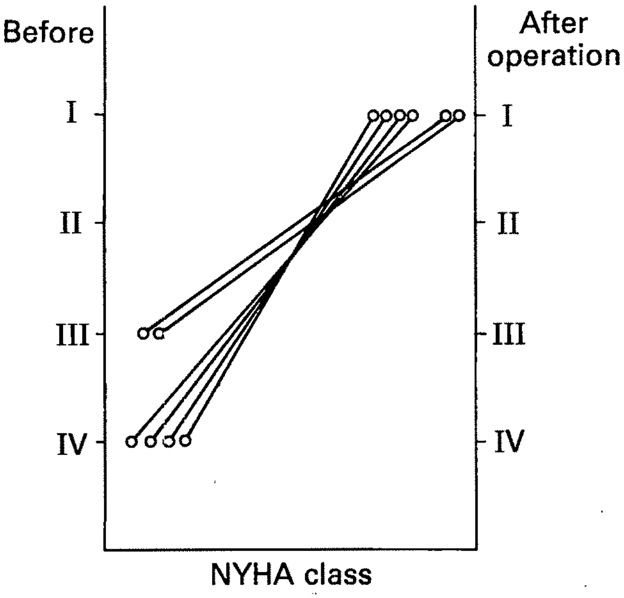

Fig 2. New York Heart Association (NYHA) functional class before and after operation.

aortic incompetence with an associated grade 2/6 murmur of aortic incompetence present. Neither of the patients with extensive aortic root abscess had more than trivial aortic incompetence. No patient had a detectable systolic gradient across the homograft valve.

Comment

Although the incidence of persistence of infection after prosthetic aortic valve replacement for endocarditis is as low as 3% to 4% in some series, this complication and paravalvular leak and valve dehiscence are still major causes of morbidity that can be influenced by improvements in surgical technique. Many patients with endocarditis do not have aortic annular involvement and can have secure placement of a prosthetic valve with a low risk of persistent infection, but in others with more advanced invasive infection, involvement of the aortic annulus, ventricular septum, and aortic root can greatly complicate valve replacement and increase the risk of valve reinfection and valve dehiscence. Annular abscess has been reported in 41% of patients dying of native aortic valve infections [8] and some degree of annular necrosis and abscess was described in all patients dying of infection of prosthetic heart valves in one series [9].

Although debridement and primary suture closure of a small aortic root abscess is possible in conjunction with valve replacement, with large annular abscesses with aortic root defects simple valve replacement is usually not possible and more complex techniques are required. These have included prosthetic patch closure of the aortic root defect with valve fixation in part to the patch [10–13], composite prosthetic valve conduit placement with reimplantation of the coronary ostia [14, 15], ascending aortic prosthetic valve placement with supravalvular coronary artery vein grafts [16–18], and extraanatomical bypass with an apicoaortic conduit [19, 20].

Lau and associates [21] first reported using the human aortic homograft to replace the entire aortic root with reimplantation of the coronary ostia for aortic valve endocarditis and aortic root abscess, and Okita and coworkers [22] later reported a 22.6% operative mortality and a 4.4% reinfection rate with this technique. This approach has the advantage of leaving the homograft valve entirely supported by the retained full circumference of the aortic wall, thus assuring normal valve function and permitting the distal suture line to be placed in uninvolved recipient aortic wall.

We believe that most of the advantages of homograft root replacement can be realized with proper trimming of the homograft to close the entire defect securely while avoiding the need for reimplantation of the coronary arteries and minimizing the amount of homograft aortic wall used. The goal, therefore, is to allow reinforcement of the abscess-created defect and replacement of the valve with preservation of all viable native root tissues. Although homograft aortic valve replacement has been advised for aortic valve endocarditis [7], there may be reluctance to use it in the presence of abscess cavities involving the aortic root for fear that geometric distortion of the homograft valve may result. Kirklin and colleagues [23] recently reported 3 patients with aortic root abscesses at and above the level of the annulus; 1 of the 3 patients had an additional abscess below the annulus of the right cusp. Each of these patients was managed using aortic wall of the homograft to cover the abscess cavity. In their discussion, Kirklin and colleagues suggest placing the entire proximal suture line well below the annular level if an extensive subannular abscess cavity exists, as it did in our patients 4 and 6 (see Table 1; Fig 1), but none of their patients had such abscess cavities. Barratt-Boyes has used a pericardial patch to cover a subannular abscess cavity, allowing the proximal suture line to be placed at the usual level. We believe that appropriate trimming of the homograft mitral valve tissue will allow reconstruction of nearly all of these subannular defects without need for an additional patch.

This small series represents a preliminary experience with the viable cryopreserved aortic homograft in the treatment of active aortic valve endocarditis, especially with aortic root abscess. We are most impressed with the flexibility afforded by the nature of this prosthesis. As shown in Fig 1, the homograft is supplied as an aortic root preparation with intact anterior leaflet of the mitral valve, aortic valve, and ascending aorta, which can be appropriately trimmed to leave the amount of homograft tissue needed to obliterate or cover defects created by the active infection. Even a ventricular septal defect adjacent to the aortic annulus could be repaired using the attached tissue from the anterior leaflet of the mitral valve.

The technique of homograft valve insertion is well described, but in our experience is substantially more difficult than mechanical or heterograft valve replacement, as reflected by our relatively long cross-clamp times. This resulted from our inexperience with the technique as well as the need for custom fitting the valve to the abnormal valve annulus created by active infections. With current techniques of myocardial protection, especially in this group of patients without coronary artery disease, these cross-clamp times appear to be tolerated well.

We agree with the recommendation of Kirklin and Barratt-Boyes [7] that the aortic homograft, because of its apparent resistance to early postoperative infection, is the valve of choice for aortic valve endocarditis. We conclude from our experience that viable cryopreserved aortic homograft is an excellent prosthesis for active aortic valve endocarditis and annular abscess due to the flexibility it gives the surgeon to readily achieve a secure repair without placement of a cloth prosthetic sewing ring in an infected annulus.

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INVITED COMMENTARY

If there is such a thing as the "seat of the soul," its location is in the vicinity of the central fibrous body. Anatomically this structure is defined as the point at which the membranous septum and the aortic, mitral, and tricuspid valves are joined in fibrous continuity. Because of the critical character of its anatomical relationships, enormous potential for harm exists when disease attacks this part of the heart. Bacterial endocarditis can be particularly devastating in this regard. Complete heart block, valvular insufficiency, fistula formation, and loss of cardiac substance are all potential problems accompanying infection in the root of the aorta. Thus, one is immediately attracted to any suggestion that there may be a better way of dealing with this devastating clinical problem.

Zwischenberger, Shalaby, and Conti have presented a series of 6 patients with active aortic valve endocarditis, 2 of whom had aortic root subvalvar abscess formation, treated with cryopreserved allograft valve replacement. As a result of this experience, these investigators suggest that such an approach offers definite advantages over synthetic valve implantation. Specifically, such grafts are believed to be more resistant to infection, and they can be custom fitted to the abnormal aortic root.

Indeed, intuitively one might think that bioprostheses in general would be superior to synthetic valves, but this has not proved universally true. Whether cryopreserved allografts will behave differently is not yet clear. The study cited by O'Brien and associates [6] suggests that such grafts may offer some protection from infection; however, even in this large series, the overall reinfection rate was in the range of 1% to 4%. Of the patients reported in the present study, 1 of 6 suffered reinfection; clearly, no bacteriological panacea has been discovered. What is noteworthy is the low incidence or complete lack of early reinfection in either study, suggesting that the early phase of the bimodal reinfection curve may be abolished. However, close scrutiny of the series of O'Brien and associates shows that this apparent effect on the infection hazard function was independent of the preservation technique (ie, allografts cryopreserved at −190°C versus fresh allografts stored at 4°C). Therefore, caution must be exercised in attributing special bacteriostatic properties to the cryopreserved tissues.

Similarly thoughtful consideration is required before completely discarding relatively straightforward, time-tested techniques in favor of a complex undertaking that is not readily accessible to every well-trained cardiothoracic surgeon. Without a doubt, the flexibility afforded by use of the allograft can be advantageous under these and other circumstances. Unfortunately, for a variety of reasons, not the least of which is the donor problem, allografts are not widely available. Because patients with aortic valve endocarditis often are in extremis and require urgent operative intervention, they cannot safely be transferred to another center with an adequate selection of allografts. In addition, the learning curve associated with this technique is predictably rather steep. Prolonged pump runs and two- to three-hour cross-clamp times are not necessarily in the best interest of these sometimes desperately ill patients. Thus, this technique so ably described by Zwischenberger and co-workers is not easily applicable under every circumstance.

Synthetic valves or stent-mounted bioprostheses continue to serve our patients well. Because of their widespread availability and ease of insertion, they will not and should not be quickly abandoned. At the same time, I acknowledge that better solutions to this difficult problem may exist, and I look to a future in which society will alleviate our donor problems and the science of immunology will allow xenogeneic transplantation. Perhaps then all will have the benefit of widespread availability of tissue valves.

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Transdiaphragmatic Implantation of the Automatic Implantable Cardioverter Defibrillator

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A new surgical approach for implantation of the automatic implantable cardioverter defibrillator without thoractomy was used in 12 patients, aged 46 to 72 years. Preimplantation arrhythmia was ventricular tachycardia in 7 patients and ventricular fibrillation in 5 patients. The mean ejection fraction was 19%. Six patients were at high risk for general anesthesia for a variety of medical problems, and 2 patients had had a previous cardiac operation. Epidural anesthesia was used in 8 patients without intubation. The surgical approach used a longitudinal epigastric extraperitoneal incision with access to the heart through an incision made in the central tendon of the diaphragm. Two patches and two epicardial sensing leads were placed in all patients. All patients but one could be defibrillated with 20 J or less. There was no operative mortality and minimal morbidity. There were two late deaths due to heart failure. Thus, the transdiaphragmatic approach provides an excellent exposure for automatic implantable cardioverter defibrillator implantation, avoids general anesthesia and thoracotomy, and can be used after a previous cardiac operation.

(Ann Thorac Surg 1989;48:371–5)

Automatic implantable cardioverter defibrillators (AICDs) are capable of recognizing and terminating malignant ventricular tachyarrhythmias [1–3] and have been shown to decrease mortality in select groups of patients [4, 5]. Initially, the defibrillation pathway consisted of a percutaneously inserted superior vena caval electrode and an epicardial patch implanted by a limited subxiphoid approach [6]. When two patch electrodes were needed to lower defibrillation thresholds, a median sternotomy or thoracotomy was used [7–10]. We review our experience with implanting the AICD in 12 patients without thoracotomy using a transdiaphragmatic approach.

Material and Methods

Patient Population and Preoperative Evaluation

Twelve patients, 11 men and 1 woman aged 46 to 72 years (mean age, 62 years), underwent transdiaphragmatic AICD implantation between February 1986 and July 1987. The underlying cardiac disease was coronary artery disease in 10 and dilated cardiomyopathy in 2. All patients experienced life-threatening tachyarrhythmias; 7 had sustained ventricular tachycardia (5.7 ± 4.4 [mean ± standard deviation] events/patient), and 5 had ventricular fibrillation (2.2 ± 0.8 events/patient). In 10 patients, ventricular arrhythmias remained inducible during electrophysiological studies despite medical trials of at least three antiarrhythmic drugs, including amiodarone in 4 patients. In 2 patients, tachyarrhythmia could not be induced during the initial, drug-free state.

Eleven patients underwent left heart catheterization and coronary angiography. Ejection fraction was assessed in all either angiographically or by radionuclide ventriculography and ranged from 10% to 44% (mean ejection fraction, 19%). Revascularization was not indicated in the 10 patients with coronary artery disease. Two patients had had previous coronary bypass grafting; 1 of them had had previous left ventricular aneurysm resection and subsequent repair of a false aneurysm of the ascending aorta. One patient had previous myocarditis, and 1 had a permanent dual-chamber bipolar pacemaker. Eight patients were considered to be at high risk for either general anesthesia or thoracotomy, or both, because of various problems, including severe pulmonary dysfunction (forced expiratory volume in 1 second between 0.5 and 1.0 L, n = 3), a very low ejection fraction (less than 20%, n = 4), obesity (n = 3), and cirrhosis and hepatic failure (n = 1).

The Implantable System

Implantable defibrillators (Cardiac Pacemakers, St Paul, MN) that require fulfillment of rate criteria and those that require rate and morphology criteria (probability density function) were used. Two epicardial patch leads were placed in all patients. In 8 patients, two large (surface area, 27 cm^2) patch leads were placed; in 4 patients, a large and a small (surface area, 13.5 cm^2) patch lead were implanted. Two epicardial screw-in electrodes were placed for sensing of heart rate in all patients.

Operative Technique

While in the operating room, all patients had a thermodilution pulmonary artery catheter implanted. All patients received intravenous prophylactic antistaphylococcal antibiotic while in the operating room and for 24 hours after operation.

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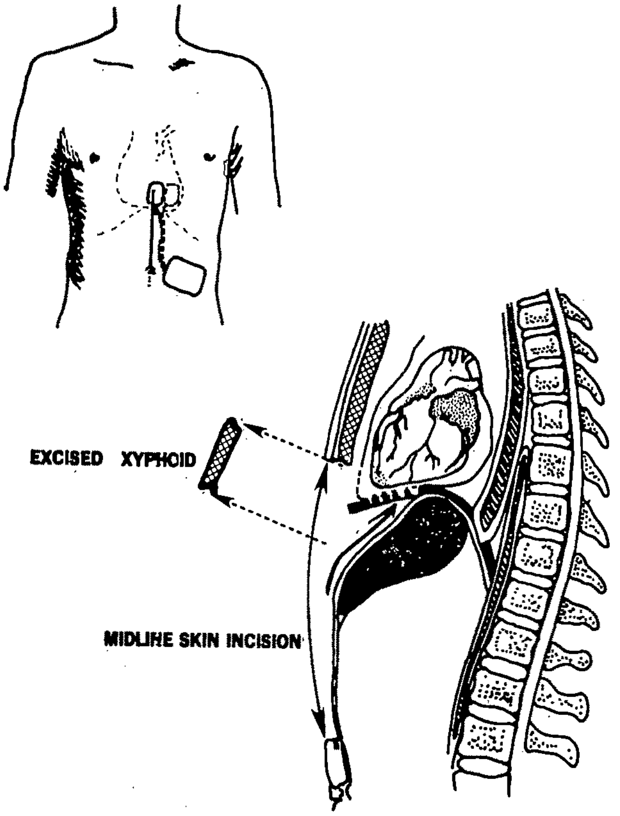

Fig 1. Extent of the midline incision, dissection of the diaphragm, and incision through the central tendon.

ANESTHESIA. Premedication consisted of morphine sulfate (5 to 10 mg) and diazepam (5 to 10 mg) administered intramuscularly. Epidural anesthesia was used in 8 patients, using bupivacaine (Marcaine) 0.5% mixed with epinephrine to a final concentration of 1:200,000 (total of 15 to 20 mL delivered). For epidural anesthesia, block up to the level of T-2 was desirable and was titrated by infusion of additional solution. Diazepam (in 2.5-mg boluses) was injected intravenously and nitrous oxide (50%) was inhaled before induction of ventricular fibrillation. General anesthesia was used in 4 patients and consisted of diazepam, fentanyl, enflurane, and nitrous oxide 50%; pancuronium was used for muscle relaxation.

EPIGASTRIC THORACOTOMY. A midline incision was made from just above the xiphosternal junction to approximately 5 cm above the umbilicus (Fig 1). The linea alba was divided, and the preperitoneal plane was exposed. The xiphoid was excised, and its diaphragmatic muscle insertion was divided. Guided by the cut ends of these muscle fibers and using a blunt dissection, we separated the caudal surface of the central tendon of the diaphragm from the parietal peritoneum for approximately 10 cm toward the spine. An anteroposterior incision was made through the central tendon and the pericardium, and the inferior wall of the heart was exposed. Exposure was further facilitated by extending the pericardiotomy in a cephalad direction behind the lower end of the sternum and by incising the central tendon leftward toward the apex of the heart (like a horizontal T). Heavy traction sutures were placed at the corners of the pericardiotomy, and a malleable retractor was placed within the pericardium for gentle caudal displacement of the upper abdominal organs while the caudal end of the sternum was lifted anteriorly by a Richardson retractor (Fig 2).

Two unipolar screw-in electrodes were inserted approximately 1 to 2 cm apart on the inferior aspect of the right ventricle. In a patient with a permanent transvenous pacemaker, the AICD sensing leads were placed distant from the pacemaker leads. Two epicardial defibrillating patches were slid into the pericardium and oriented to place maximal myocardial mass between them. One patch was placed on the anterior aspect of the heart, bridging over the interventricular groove midway between the base of the heart and the apex, and the other patch was placed on the inferior-posterior aspect of the left ventricle. When a large and a small patch were used, the large one was placed over the posterolateral aspect of the left ventricle and the smaller one was placed anteriorly over the right ventricle. The patch leads were marked near their insertion into the AICD to enable their identification at future replacement of the generator. After completion of intraoperative testing, each defibrillating electrode was secured with two sutures, one placed at the patch–lead junction and one at the corner of the patch. The anterior lead was tacked to the epicardium with 3-0 Prolene (Ethicon) pledgeted sutures, and the inferoposterior lead was secured to the pericardium (Fig 3). The sensing and defibrillating leads were then attached to the AICD generator, which was implanted into a left abdominal paramedian prefascial pouch, before final testing. The diaphragm was reapproximated with interrupted 2-0 Ethibond suture (Fig 4), and the abdominal wound was closed in layers.

Testing of the Automatic Implantable Cardioverter Defibrillator

Intraoperative testing was performed. The R wave amplitudes of the epicardial sensing and the defibrillating leads were measured during sinus rhythm according to the manufacturer's recommendations. Leads were repositioned if R wave amplitude was less than 5 mV. The defibrillating leads were then connected to the external cardioverter defibrillator. Ventricular fibrillation was induced by 60-cps direct current through the epicardial sensing leads. Defibrillating countershocks were delivered by the patch electrodes through the external cardioverter defibrillator. Ability to defibrillate with an energy of 20 J or less was considered an acceptable margin of safety. All four leads were then connected to the AICD, and ventricular fibrillation was again induced and was automatically terminated by the AICD at the discharge energy (25 to 32 J) preset by the manufacturer. A standard external defibrillator with sterile internal paddles was always available on the operating field to back up the external cardioverter defibrillator or the AICD. Before each patient was discharged from the hospital, the ability of the AICD system to defibrillate the patient was tested.

Results

In all patients, two epicardial leads and two defibrillator patches were attached to the heart and, when necessary,

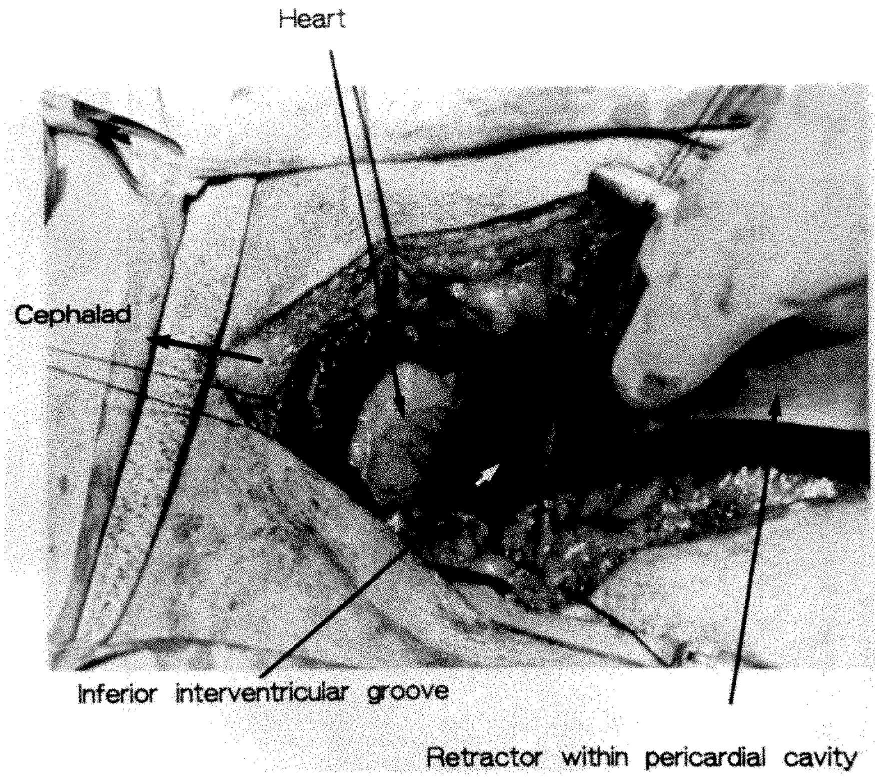
Heart
Cephalad
Inferior interventricular groove
Retractor within pericardial cavity

Fig 2. Inferior aspect of the heart exposed through the diaphragm.

repositioned, through the diaphragmatic incision. There were no operative deaths and no perioperative myocardial infarctions. In the 2 patients who had undergone a previous heart operation and in the 1 patient with myocarditis, the adhesions covering the inferior, posterior, and lateral aspects of the heart could be divided by mostly blunt dissection, with some sharp dissection. No patient required blood transfusion and none required reexploration for bleeding.

In 8 patients, epidural anesthesia was successfully applied without adverse effects. These patients were comfortable throughout the procedure. Postoperative pain was controlled by a single dose of morphine sulfate (2 to 6 mg) injected intravenously, followed by oral acetominophen plus codeine (30 mg) for 24 to 48 hours. Five of the 8 patients receiving epidural anesthesia were fed and ambulating several hours after operation. Three patients were intubated after returning to the intensive

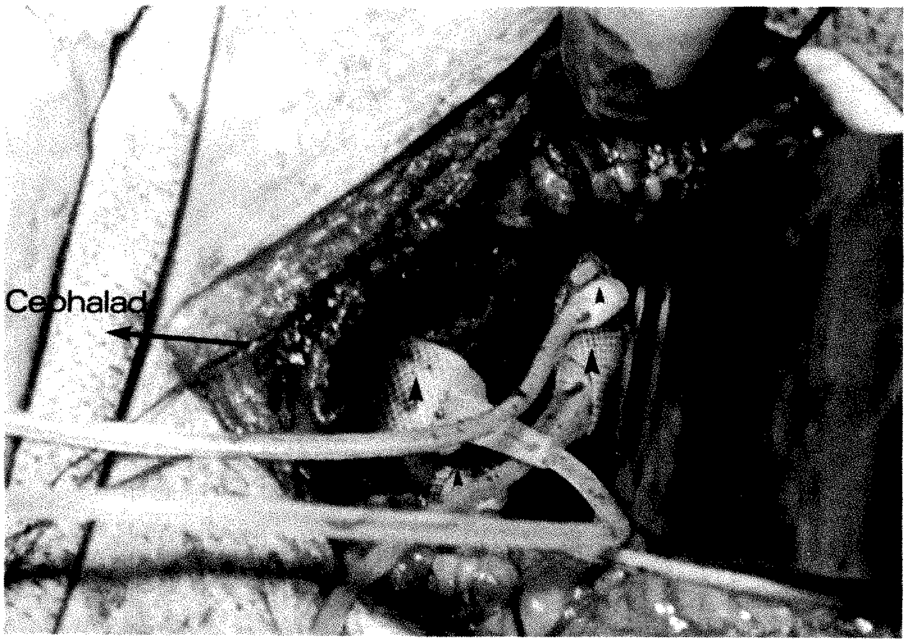

Fig 3. Two epicardial patch leads (large arrowheads) *and two unipolar screw-in leads* (small arrowheads) *were placed.*

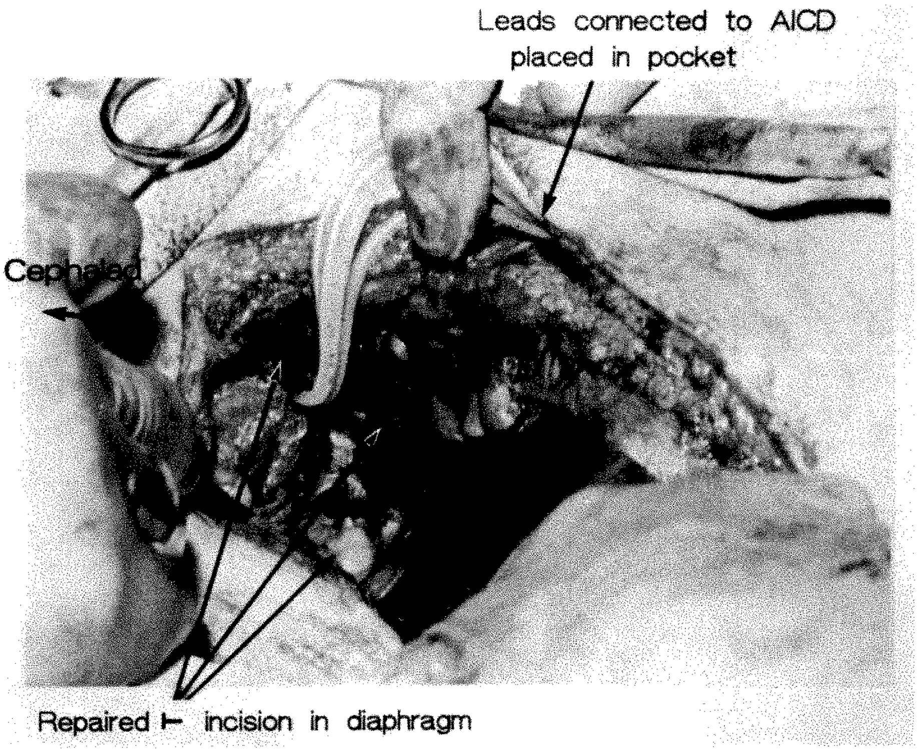
Leads connected to AICD placed in pocket
Cephalad
Repaired ⊢ incision in diaphragm

*Fig 4. Diaphragmatic incision after repair. (*AICD = *automatic implantable cardioverter defibrillator.)*

care unit, 1 as a result of congestive heart failure and 2 for treatment of severe bronchospasm.

At intraoperative testing, mean bipolar R wave on the bipolar leads was 10.7 mV (range, 6 to 18 mV) and on the patch leads, 11.5 mV (range, 6 to 20 mV). Successful defibrillation was accomplished in 5 patients with 15 J and in 5 others with 20 J. One patient required 30 J for defibrillation (described later in this section). In 1 patient, AICD implantation was aborted due to incessant ventricular tachycardia.

There were two intraoperative complications, neither of which was related to the surgical technique. A possibly malfunctioning unit was removed and replaced the next day under local anesthesia after it recharged and discharged without obvious reason. In 1 patient, an induced ventricular tachycardia was incessant despite multiple attempted cardioversions. Multiple antiarrhythmic agents were tried without success. Amiodarone administered intravenously (1.0 g over 10 min) caused conversion to sinus rhythm. All patches and leads were removed to avoid question of mechanical factors contributing to the tachycardia. The patient was maintained on amiodarone and had an uneventful recovery.

Two patients required reoperation, but only one reoperation required entry into the chest. In the first patient, a probability density function device had to be changed to a rate-sensing device as it was shown not to sense all ventricular tachycardia morphologies. Furthermore, change in polarity of the patches from left ventricular patch as anode and right ventricular patch as cathode to the opposite caused the energy required for cardioversion of fibrillation to be reduced from 30 to 20 J. In the second patient, chest roentgenograms and cardiac fluoroscopy revealed dislodgement of one of the patches after unsuccessful predischarge testing. At reoperation, the 5-0 Prolene suture that held the patch to the pericardium pulled through. The patch was replaced by a large patch, repositioned, and tacked down as described. Subsequently, the defibrillating threshold was acceptable.

In 2 patients a large fluid collection developed in the pulse generator pocket, without signs of local inflammation, along with pericardial effusion and ankle edema. The AICD failed to terminate ventricular fibrillation at predischarge testing in 1 of these patients. When both patients were treated with diuretic agents and steroids for 1 week, the pocket seroma and pericardial effusion resolved. Retesting after resolution of the pericardial effusion showed successful defibrillation. All other units were functioning well at predischarge testing.

Follow-up was available in all patients, and ranged between 2 and 18 months (mean follow-up, 8.3 months). Ten patients are alive and well; 2 died of heart failure at 2 and 10 months, respectively. In no patient was lead dislodgement or change in position noted on chest radiograms. None had skin erosion or infection. Six units discharged between 1 and 10 times, for a total of 18 discharges.

Comment

The AICD was developed for treatment of patients at high risk of sudden death due to ventricular tachyarrhythmia [1]. Early clinical evaluations have shown that the device is capable of recognizing malignant ventricular tachyarrhythmia and promptly charging and delivering an electrical discharge to restore normal rhythm [2, 3]. Life-table analysis based on data accumulated since the inception of clinical application of the device in 1980 demonstrated that the AICD significantly reduced the risk of arrhythmic death in patients with refractory ventricular tachyarrhythmias [4, 5].

A few surgical techniques have been used for implantation of the device. Median sternotomy has been the preferred method when defibrillator implantation is combined with other cardiac procedures [7]. Because of the excellent exposure of the heart with this approach, it has also been preferred for isolated defibrillator implantation [8, 10]. For patients who have had previous cardiac surgical procedures, the left anterior thoracotomy has been used with extrapericardial placement of the patch, to avoid dissection of scar tissue and adhesions associated with median sternotomy [6]. However, both these approaches may be associated with substantial morbidity and complications that may follow major thoracic procedures. The subxiphoid technique [6], in which a small skin incision and a window in the anterior aspect of the pericardium above the diaphragmatic reflection are used, was introduced as a method with low morbidity by which one or two patches can be placed [11]. However, this method provides a limited exposure, which may affect the risk of the procedure.

Like Lawrie and associates [9], we sought a technique that would provide good exposure with minimal morbidity. The transdiaphragmatic approach is technically simple and safe and is associated with minimal morbidity. It provides ample exposure for implantation of two large patches that can be repositioned as deemed necessary. A previous cardiac operation did not create any appreciable difficulties, probably because the heart was approached from an area usually covered by soft and easily dissectable adhesions. This approach is applicable to very sick patients with poor left ventricular function and severe pulmonary dysfunction. With epidural block, the patients remain awake throughout the operation and need not be intubated; such block can also reduce the hormonal and metabolic stress associated with general anesthesia [12]. Because thoracotomy is avoided, postoperative pain is easily controlled and the risk of pulmonary complications is reduced. We found this approach to be somewhat more difficult only in patients with hypermorphic body structure, in whom the chest is narrow and the diaphragm is higher than the lower edge of the rib cage.

Postoperative intubation was related only to baseline pulmonary or left ventricular dysfunction. Intubations lasted less than 24 hours while underlying problems were treated. We believe that pulmonary morbidity would have been prohibitive if we had performed thoracotomy in these patients.

The few complications in this group illustrate the importance of securing each patch in at least two different points to prevent migration or rotation, and show that pericardial fluid cannot affect the energy needed for defibrillation. Pericardial fluid has been reported to lower the electrical impedance between the patches, thus requiring more energy to defibrillate patients [13]. As a pocket seroma can often be expected [4, 14], it is advisable to consider testing of the device or treatment of the fluid collection when a large fluid collection is observed.

Our experience with the transdiaphragmatic technique for implantation of AICD in 12 patients has been encouraging. This approach provides good exposure, can avoid general anesthesia and thoracotomy, and is associated with minimal morbidity. The operation is well tolerated by very sick patients. We consider it our primary approach for isolated AICD implantation.

We gratefully acknowledge Elizabeth Worthington for her skillful artwork, and Woo Park, MD, for his description of the anesthesia.

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Longevity of Expanded Polytetrafluoroethylene Grafts for Superior Vena Cava

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We previously reported that the expanded polytetrafluoroethylene (ePTFE) graft for superior vena cava (SVC) substitution presents the problems of flexion and kinking when the graft is long. We therefore replaced the SVC of dogs with two types of prosthetic substitutes, ePTFE (Gore-Tex) and spiral-supported ePTFE (Im/praflex), and evaluated the long-term patency of the prosthetic substitutes. Total replacement of the SVC was performed in 9 adult mongrel dogs. The substitutes were ePTFE and spiral-supported ePTFE in 5 and 4 dogs, respectively. The animals were killed about 3 years after replacement of the SVC, and the harvested specimens were histologically examined by light microscopy and scanning electron microscopy. Evaluation of ePTFE revealed late occlusion in 1 of 5 dogs. The spiral-supported ePTFE showed patency in all dogs. In the group with ePTFE grafts, light microscopic examination revealed abnormalities of endothelial cells, granulation, and necrosis. There was no hyperplasia of the subendothelial connective tissue near the center. In the animals with spiral-supported ePTFE grafts, the subendothelial connective tissue showed favorable growth even in the center of the reconstructed site. There was no granulation in the spiral-supported ePTFE group. Scanning electron microscopic examination in the ePTFE group showed that endothelial cells were spindle-shaped and had an irregular surface. The spiral-supported ePTFE group showed an almost regular form of endothelial cells and no abnormalities except for the slightly spindled shape in the center. Therefore, we recommend that spiral-supported ePTFE should be used as an SVC substitute in clinical situations.

(Ann Thorac Surg 1989;48:376–80)

In our institution, we performed total replacement of the superior vena cava (SVC) using an expanded polytetrafluoroethylene (ePTFE) graft in a patient with malignant mediastinal tumor and the substitute shows patency at more than 7 years after the operation [1]. This case suggests that ePTFE substitutes for the SVC have sufficient potential quality. However, the ePTFE graft showed kinking in this patient, requiring investigation of materials for ePTFE that have some supporting ability. Actually, some types of ePTFE had been used clinically, but longevity of the ePTFE substitutes for SVC had not been reported. We therefore replaced the SVC in dogs with two types of prosthetic substitute, ePTFE (Gore-Tex) and spiral-supported ePTFE (Impraflex), and evaluated the long-term patency of the prosthetic substitutes more than 3 years after the operation.

Table 1. Long-Term Patency of Grafts

Graft Material	Observation Period (mo)	Patency	Granulation	Neointimal Growth	Endothelial Irregularity
Gore-Tex					
1[a,b]	30	−	+	. . .[c]	. . .[c]
2[d]	33	+	−	+	+
3[d]	34	+	+	±	+++
4[d]	34	+	+	+	+
5[d]	41	+	+	±	++
Impraflex					
1[a]	36	+	−	+	−
2	36	+	−	+	−
3	36	+	−	+	−
4[e]	39 (continuing)	+	. . .[c]	. . .[c]	. . .[c]

[a] Neointimal growth and granulation were examined by light microscope. [b] The late obstruction case; the cavogram performed 1 year after operation showed patency of the graft. [c] Not examined. [d] Endothelial irregularity as examined by scanning electron microscope. [e] This dog is being kept alive for examination after a further 5-year period.

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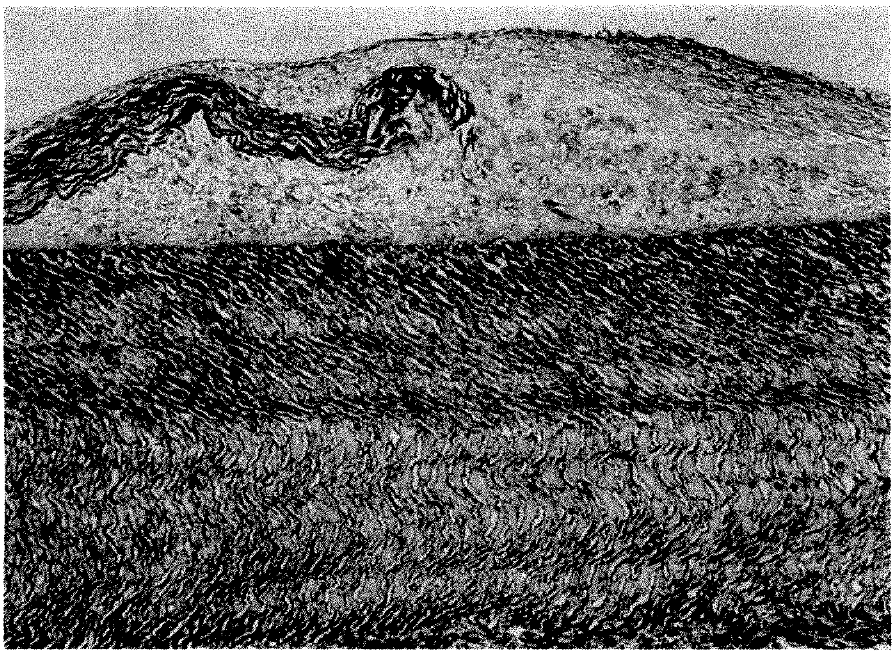

Fig 1. Whitish granulation tissue was present in the vicinity of the site of anastomosis and the center of the reconstructed site after replacement of the superior vena cava with an expanded polytetrafluoroethylene graft. Staining for fibrin revealed that the mass of fibrin in the center of the reconstructed site was surrounded by collagen fibers showing hyperplasia.

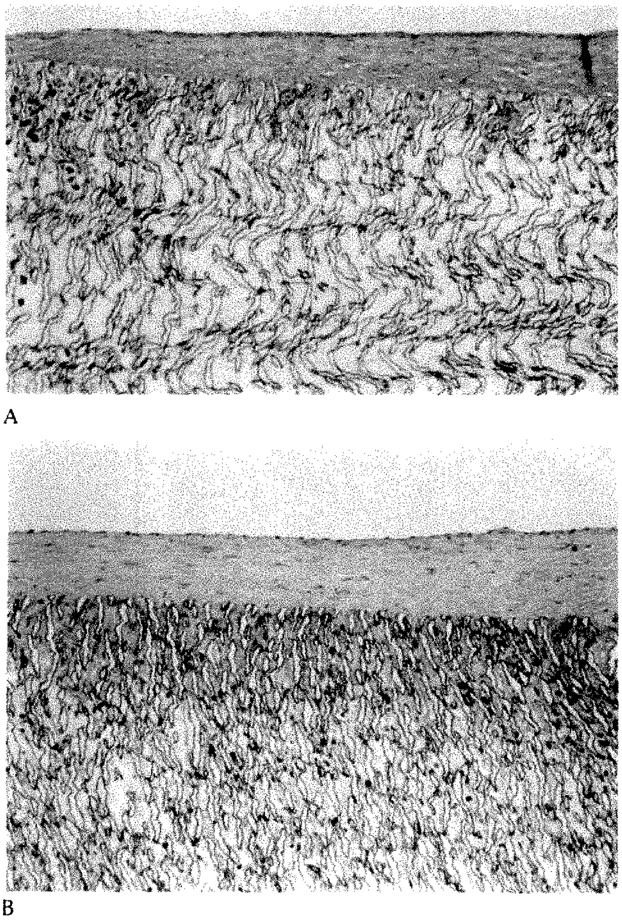

Fig 2. The group with spiral-supported expanded polytetrafluoroethylene grafts showed good hyperplasia of the subendothelial connective tissue even in the center of the reconstructed site, and only a slight difference in the degree of hyperplasia between the vicinity of the site of anastomosis and the center. No granulation was observed. (A) Site of anastomosis; (B) center of reconstructed site.

Material and Methods

Total replacement of the SVC was performed in 9 adult mongrel dogs weighing 11 to 15 kg. The substitutes were ePTFE and spiral-supported ePTFE in 5 and 4 dogs, respectively. Each substitute was 3 cm in length, because the length of the SVC in this experimental series was short, and had an internal diameter of 10 mm. Reconstruction was performed by a continuous suturing procedure with two-point stay using 5-0 Prolene sutures in accordance with the clinical experience in our institute. These animals did not receive any anticoagulation therapy. They were killed about 3 years after replacement of the SVC, and the harvested specimens were histologically examined by light and scanning electron microscopy. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

Patency

Evaluation of the ePTFE grafts 30 to 41 months (mean, 34.4 months) after the operation revealed occlusion in 1 of the 5 dogs. In this dog, patency of the ePTFE, without kinking, was shown by angiography 1 year after reconstruction, but late occlusion due to granulation at the anastomosed site was evident. The spiral-supported ePTFE showed favorable patency in 3 dogs 36 months after operation, and the remaining dog is being kept alive for examination after a further 5-year period (Table 1).

Light Microscopic Findings

In the group with ePTFE grafts, whitish granulation tissue was observed in the immediate vicinity of the anastomosed site and in the center of the reconstructed site. Histological examination revealed abnormalities of endo-

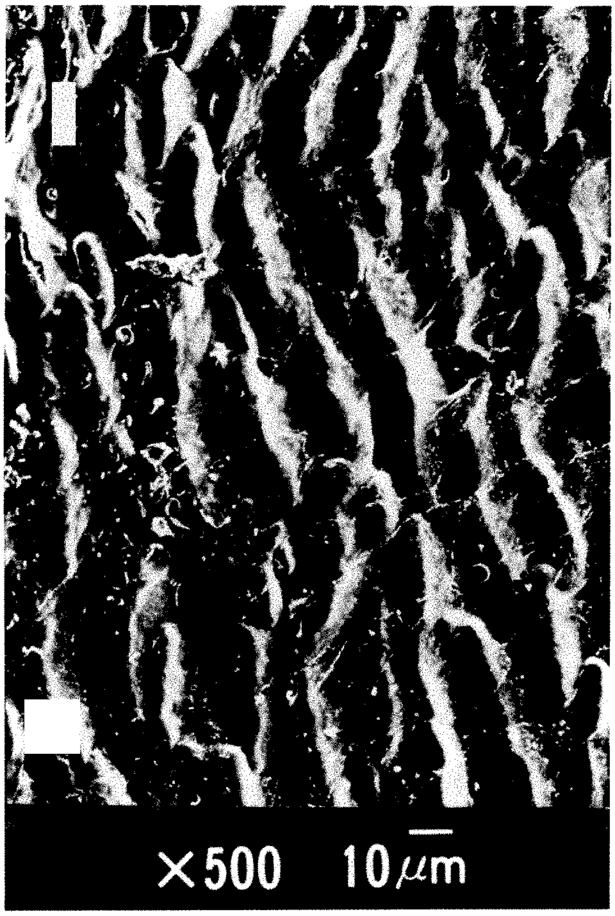

Fig 3. Scanning electron microscopic findings in the group with expanded polytetrafluoroethylene grafts showed deformation (spindle shape) of endothelial cells, with no sharp demarcation of the cells and an irregular surface. (×500 before 30% reduction.)

thelial cells, precipitation of fibrin, granulation, and necrosis accompanying cellular infiltration (Fig 1). The occlusion observed in 1 animal was caused by late granulation at the anastomosed site. There was no hyperplasia of the subendothelial connective tissue near the center of the reconstructed site, and endothelial cells arranged in a layer were present just above the ePTFE.

In the animals with spiral-supported ePTFE grafts, on the other hand, the subendothelial connective tissue showed favorable growth even in the center of the reconstructed site, with a slight difference in the degree of growth between the center and the vicinity of the anastomosed site. There was no granulation in the spiral-supported ePTFE group (Fig 2).

Electron Microscopic Findings

In the ePTFE group, endothelial cells were spindle-shaped, unlike the original rhombic-shaped cells, even in the vicinity of the anastomosed site where the pseudointima showed good development, and the cells showed no sharp demarcation, with separation and irregular surface features (Fig 3). The spiral-supported ePTFE group showed an almost regular form of endothelial cells and no abnormalities except for the slightly spindle-shaped cells in the center of the reconstructed site (Fig 4).

Comment

There have been few reports on reconstruction of the SVC for malignant tumors of the mediastinum and lung [2–4], and careful consideration still argues against the procedure, particularly that of total replacement associated with tumor resection. In our institution, however, total replacement of the SVC was performed for invasive thymoma, and we have confirmed the patency of the reconstructed site 7 years after operation [1]. According to Dartevelle and colleagues [5], who reported 13 cases of replacement for malignant tumors of the mediastinum and lung, 27% of patients achieved 3-year survival. If the indication is strictly limited, the therapeutic effect of SVC reconstruction will improve.

Autologous veins [6–8], pericardium [9, 10], and ePTFE [11–15] have been used clinically as SVC substitutes, and ePTFE has been used in many recently reported trials [1,

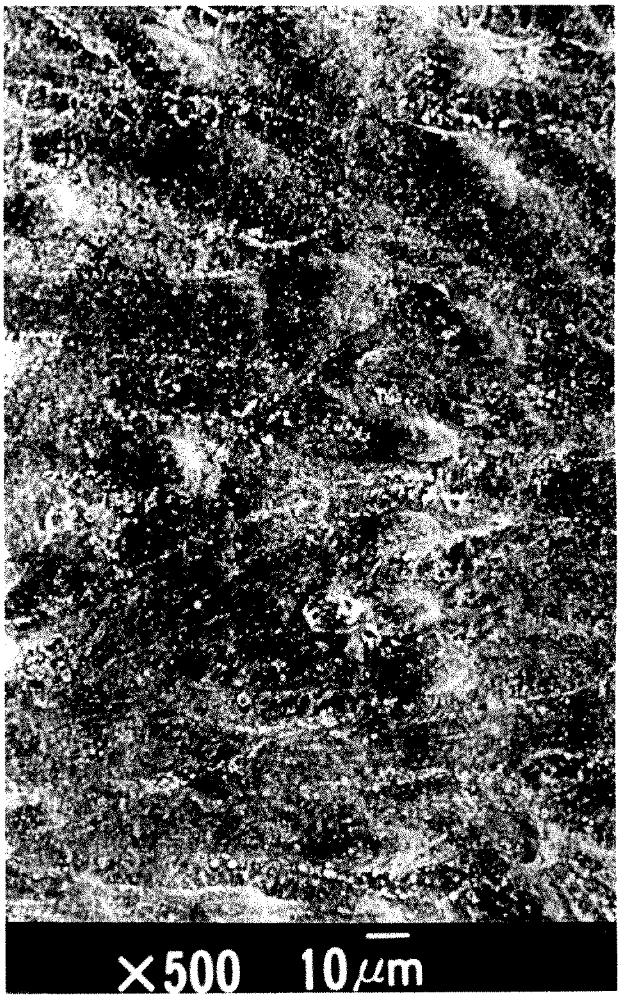

Fig 4. There were no abnormal electron microscopic findings in the group with spiral-supported expanded polytetrafluoroethylene grafts except for slightly spindle-shaped endothelial cells in the center of the reconstructed site. (×500 before 29% reduction.)

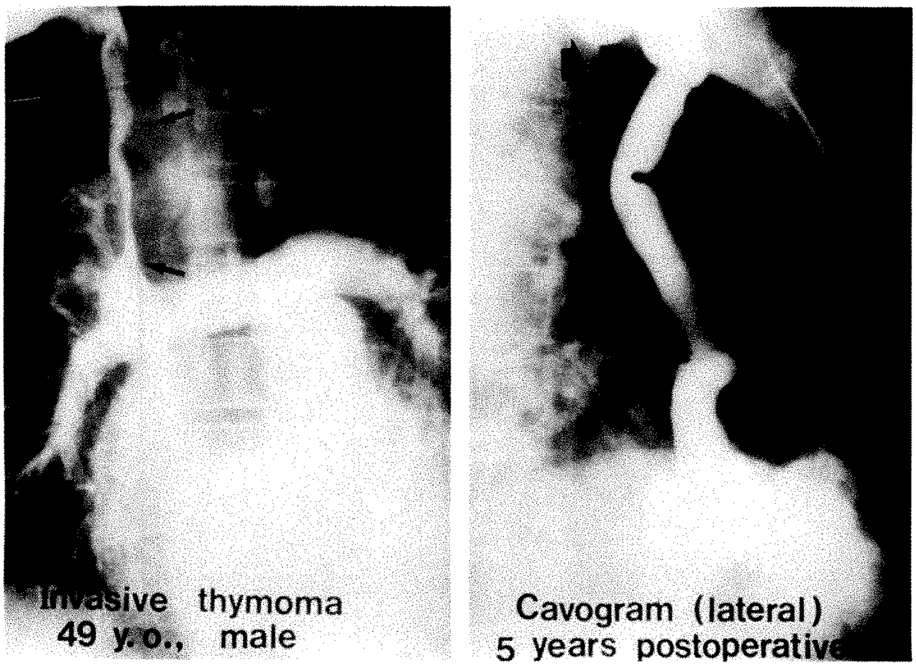

Fig 5. Preoperative cavogram and cavogram performed 5 years after operation. Reconstructed graft (expanded polytetrafluoroethylene grafts) showed strong kinking. Functional patency was tolerable, but the long-term patency of the antikinking substitute for superior vena cava must be determined.

5] with good results. However, as we have already reported, ePTFE presents the problems of flexion and kinking when the area of reconstruction is long (Fig 5). The type of ePTFE to be used clinically must be investigated over a long term. The most important observation in the present study comparing spiral-supported ePTFE with ePTFE was the late occlusion of the nonsupported ePTFE graft, which was not due to kinking but to excessive granulation at the site of anastomosis. The condition was considered to have been caused by uneven hyperplasia of the subendothelial connective tissue. In contrast, the spiral-supported ePTFE graft induced even growth of the subendothelial connective tissue at the site of anastomosis and in the center of the reconstructed site, showing no excessive granulation.

Fiore and co-workers [14], studying short-term patency of spiral-supported ePTFE grafts, obtained no difference in the patency rate of the SVC. There was, however, a difference in the patency of the inferior vena cava (for which reconstruction yielded poor results), with the patency rate with Impraflex being better than that with Gore-Tex. According to Dartevelle and colleagues [5], who investigated the usefulness of ePTFE for reconstruction of the SVC (the synthetics used in practice are considered to have some supporting ability), the rate of patency was 92% 1 year after the operation, possibly indicating that the synthetics they used in practice yielded no problem for short-term patency and can be expected to be effective in reconstructive use. However, reports on long-term patency also indicate that to prevent late granulation, use of ePTFE of smaller pore size as an SVC replacement is desirable; conventional ePTFE has a relatively large pore size (30 μm). Gore-Tex is a reinforced type with an inner layer of 20-μm pore size and an outer layer of very small pore size (10 μm). On the other hand, Impraflex has a one-piece structure of about 20-μm pore size. These factors are the main reason for the differences in these experimental data. In addition, when the area of reconstruction was long, blood circulatory disorders occurred due to flexion of the ePTFE [1]. Therefore, use of spiral-supported ePTFE (Impraflex) appears desirable. Adequate observation is also necessary to ascertain long-term patency [16].

In conclusion, long-term patency 3 years after reconstruction of the SVC with ePTFE and spiral-supported ePTFE was studied in dogs; late occlusion due to granulomatous stenosis at the anastomosed site was observed when reconstruction was performed with ePTFE. Only 1 of 9 dogs had late graft occlusion, which is a high patency rate at 3 years.

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Notice From the American Board of Thoracic Surgery

The part 1 (written) examination will be held at the Hyatt-Regency, Dallas Fort Worth Airport, Dallas TX, on February 3, 1991. The closing date for registration is August 1, 1990.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

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WARNING

It is recommended that Blenoxane be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Pulmonary fibrosis is the most severe toxicity associated with Blenoxane. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with Blenoxane.

DESCRIPTION

Blenoxane (sterile bleomycin sulfate, U.S.P.) is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of **Streptomyces verticillus.** It is freely soluble in water.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.

ACTION

Although the exact mechanism of action of Blenoxane is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

In mice, high concentrations of Blenoxane are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have been found to have high concentrations of Blenoxane in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of Blenoxane found in bone marrow may be related to high levels of Blenoxane degradative enzymes found in that tissue.

In patients with a creatinine clearance of > 35 mL per minute, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of < 35 mL per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. In humans, 60 to 70% of an administered dose is recovered in the urine as active bleomycin.

INDICATIONS

Blenoxane should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:

Squamous Cell Carcinoma–Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingiva, epiglottis, larynx), skin, penis, cervix, and vulva. The response to Blenoxane is poorer in patients with head and neck cancer previously irradiated.

Lymphomas–Hodgkin's, reticulum cell sarcoma, lymphosarcoma.

Testicular Carcinoma–Embryonal cell, choriocarcinoma, and teratocarcinoma.

CONTRAINDICATIONS

Blenoxane is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

WARNINGS

Patients receiving Blenoxane must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by Blenoxane progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended.

Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of lymphoma patients treated with Blenoxane. Since these usually occur after the first or second dose, careful monitoring is essential after these doses.

Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Usage in Pregnancy: Safe use of Blenoxane in pregnant women has not been established.

ADVERSE REACTIONS

Pulmonary–This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to Blenoxane has been extremely difficult. The earliest symptom associated with Blenoxane pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, Blenoxane-induced pneumonitis produces nonspecific patchy opacities, usually of the lower lung fields. The most common changes in pulmonary function tests are a decrease in total lung volume and a decrease in vital capacity. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to Blenoxane toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific, e.g., similar changes are seen in radiation pneumonitis, pneumocystic pneumonitis.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1 to 2 weeks. If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Recent studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{CO}) during treatment with Blenoxane may be an indicator of subclinical pulmonary toxicity. It is recommended that the DL_{CO} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DL_{CO} falls below 30 to 35% of the pretreatment value.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations than usually would be considered safe. Suggested preventive measures are:

(1) Maintain $FI\ O_2$ at concentrations approximating that of room air (25%) during surgery and the postoperative period.
(2) Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during Blenoxane infusions. Although each patient must be individually evaluated, further courses of Blenoxane do not appear to be contraindicated.

Idiosyncratic Reactions–In approximately 1% of the lymphoma patients treated with Blenoxane, an idiosyncratic reaction, similar to anaphylaxis clinically, has been reported. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose. It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic including volume expansion, pressor agents, antihistamines, and corticosteroids.

Integument and Mucous Membranes–These are the most frequent side effects being reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue Blenoxane therapy in 2% of treated patients because of these toxicities.

Skin toxicity is a relatively late manifestation usually developing in the 2nd and 3rd week of treatment after 150 to 200 units of Blenoxane have been administered and appears to be related to the cumulative dose.

Other–Vascular toxicities coincident with the use of Blenoxane in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with Blenoxane in combination with vinblastine with or without cisplatin or, in a few cases, with Blenoxane as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, Blenoxane, vinblastine, hypomagnesemia, or a combination of any of these factors.

Fever, chills, and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions were reported infrequently.

DOSAGE

Because of the possibility of an anaphylactoid reaction, lymphoma patients should be treated with 2 units or less for the first 2 doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedule is recommended: **Squamous cell carcinoma, lymphosarcoma, reticulum cell sarcoma, testicular carcinoma**–0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease–0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

Pulmonary toxicity of Blenoxane appears to be dose related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Note: When Blenoxane is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's Disease and testicular tumors is prompt and noted within two weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as three weeks before any improvement is noted.

ADMINISTRATION

Blenoxane may be given by the intramuscular, intravenous, or subcutaneous routes.

Intramuscular or Subcutaneous–Dissolve the contents of a Blenoxane vial in 1 to 5 mL of Sterile Water for Injection, U.S.P., Sodium Chloride for Injection, U.S.P., 5% Dextrose Injection, U.S.P., or Bacteriostatic Water for Injection, U.S.P.

Intravenous–Dissolve the contents of the vial in 5 mL or more of a solution suitable for injection, e.g., physiologic saline or glucose, and administer slowly over a period of ten minutes.

STABILITY

The sterile powder is stable under refrigeration (2°-8°C) and should not be used after the expiration date is reached.

Blenoxane is stable for 24 hours at room temperature in Sodium Chloride or 5% Dextrose Solution.

Blenoxane is stable for 24 hours in 5% Dextrose containing heparin 100 units per mL or 1000 units per mL.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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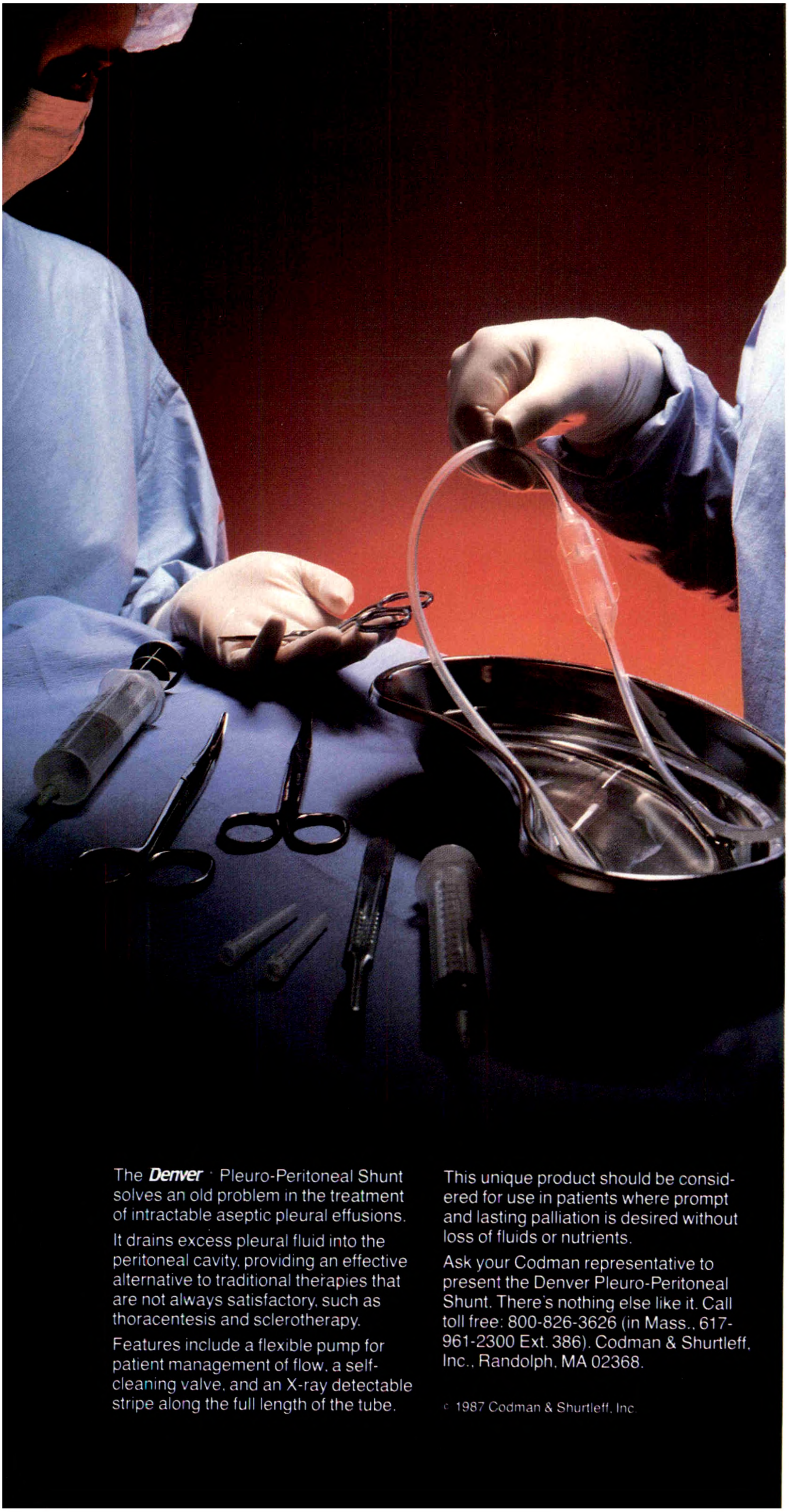

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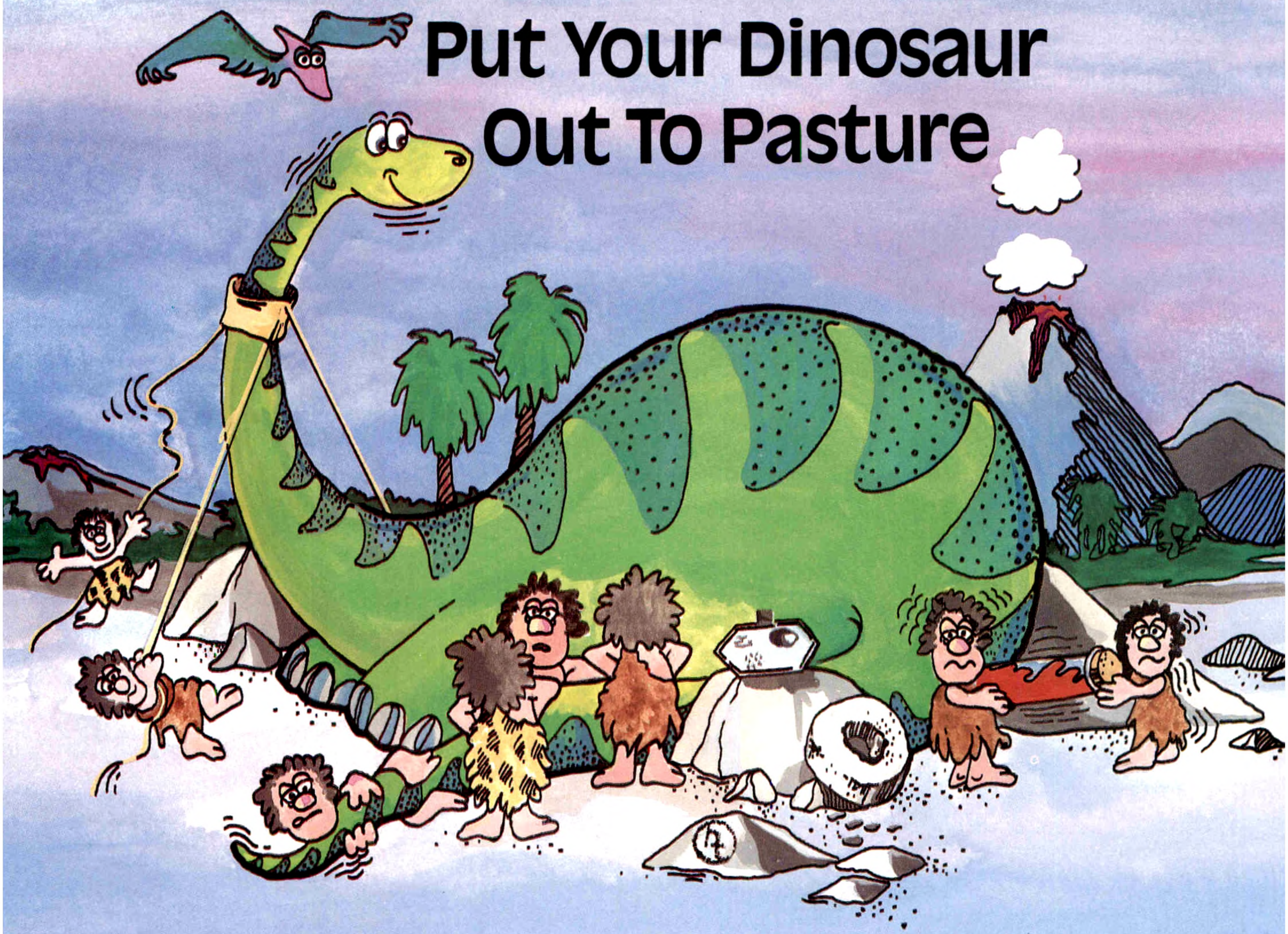

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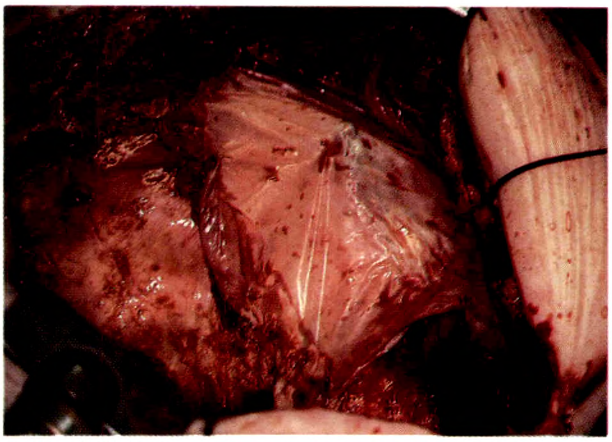

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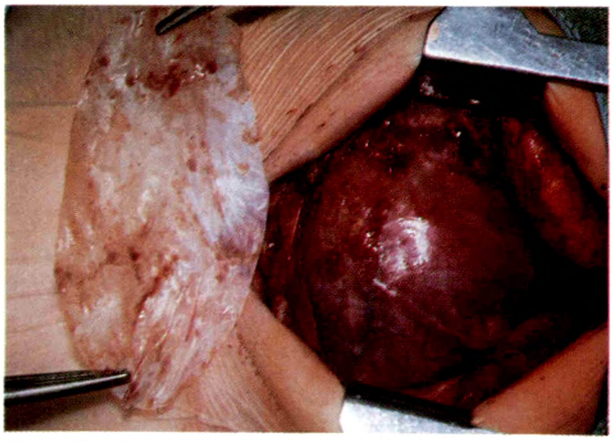

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Indications: Bioprostheses are indicated for use in patients suffering from valvular heart disease. Aortic and mitral valvular heart disease are conditions involving any of the following: obstructions of the heart valves, or stenosis; leakage of the valves, known as regurgitation or insufficiency; and combinations of the two, sometimes referred to as mixed disease or combined lesions. Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial ischemia. Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy. The Carpentier-Edwards bioprosthesis is intended for use in patients whose aortic or mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one. It is also intended for use in patients with a previously implanted aortic or mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis. **Warnings:** For Single Patient Use Only In the presence of conditions affecting calcium metabolism or when calcium-containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, in the presence of severe systemic hypertension, and in patients who are on maintenance hemodialysis The decision to use a tissue valve must ultimately be made by the physician on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient are made, and alternative methods of treatment are considered. Overall durability, especially long-term, has not been established for bioprostheses. Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of prosthetic valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery. **Note:** Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis. Caréful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall or history of previous atrial thrombosis. The appropriate anticoagulation therapy must be determined by the physician on an individual basis. **Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result. The Carpentier-Edwards bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.** Passing diagnostic catheters and transvenous pacing leads across a Carpentier-Edwards bioprosthesis could damage the valve. Consequently, it is recommended that these procedures be avoided. Both the valve and glutaraldehyde storage solution are **sterile.** The outside of the jar is **not sterile** and must not be placed in the sterile field. Furthermore, the valve and container should **never** be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation. Storage between 10°C and 25°C is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue. **Any valve that has been frozen or exposed to temperatures greater than 60°C should not be used for human implantation.** Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact, immediately flush the affected area with water. In the event of contact with eyes, seek medical attention. **Surgical Precautions: 1.** When choosing a valve for a given patient, the size, age, and physical condition of the patient in relation to the size of the prosthesis must be taken into consideration to minimize the possibility of obtaining a suboptimal hemodynamic result. The selection of a valve, however, must ultimately be made by the physician on an individual basis after carefully weighing all of the risks and benefits to the patient. **2.** Due to the relative flexibility of the frame, care must be exercised to avoid the use of too large a prosthesis to prevent folding or extreme deformation of the stent that may render the valve incompetent. Oversizing may create highly localized mechanical stresses resulting in tissue failure in the form of detachment of the leaflets or porcine aortic wall from the valve stent posts. **3.** Left ventricular perforation or ulceration has been reported. Both open and closed chest cardiac massage in patients with an open strut mitral prosthesis increases the risk of ventricular perforation. Additionally, lifting, flexing, and manual compression of the distended heart after discontinuation of bypass may cause a commissure strut to be pushed through the endocardium, producing a dissecting hematoma with subsequent uncontrolled hemorrhage. **4.** The spacing of the sutures in the remnant of the valvular orifice and the prosthesis suture ring must be carefully matched to avoid folding of the leaflets or extreme distortion of the orifice. Edwards CVS Division has received reports in which individual mattress sutures, spanning a distance of 10 to 15mm, produced a purse-string effect causing compression of the valve orifice. **5.** When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue. Cases have been reported in which bioprostheses developed severe regurgitation and had to be replaced as a result of wear due to contact with sutures. **6.** Unlike rigid mechanical valves, the stent wall is soft and will not resist needle penetration. Accordingly, extreme care must be exercised when placing sutures through the sewing margin to avoid penetration of the side wall of the stent and possible laceration of the leaflet tissue. **7.** As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised, particularly in mitral replacement, to avoid looping or catching a suture around the free legs which would interfere with proper valvular function. **8.** The stent of the bioprosthesis is asymmetrical to conform to the natural shape of the porcine aortic valve. Consequently, the commissure supports are not equidistantly spaced. The contrasting suture markers in the sewing ring of the mitral valve denote the greatest intercommissural distance. These two commissure supports should be oriented so as to straddle the ventricular outflow tract to avoid murmurs due to blood flow turbulence. **Note:** The contrasting suture material should not be removed from the prosthesis. **9.** In the aortic position, the struts should correspond to the remnants of the natural commissures so as not to obstruct the coronary ostia. **10.** A serial number tag is attached to the sewing ring of each valve by a suture. This serial number should be checked against the number on the jar; if any difference is noted, the valve should be returned unused. This tag should not be detached from the valve until implant is imminent. Care should be exercised to avoid cutting or tearing the suture ring cloth during removal. **11.** Gentle handling is required for all implantable devices. If the valve is dropped, damaged, or mishandled in any way, it must not be used for human implantation. **Complications:** As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Complications associated with the use of Carpentier-Edwards bioprostheses include stenosis; regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding diatheses related to the use of anticoagulant therapy, ventricular perforation by stent posts, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, thickening, perforation, suture abrasion, instrument trauma, and leaflet or aortic wall detachment from the valve stent posts. These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct. **Note:** Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes an apparent causal relationship between the consumption of daily calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period; and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpentier-Edwards bioprostheses to calcification as compared to other commercially available porcine valves. **Caution:** Federal (USA) law restricts this device to sale by or on the order of a physician. Baxter International Inc. is the owner of the following US patent which covers the products described herein: 4,106,129. Patent numbers in foreign countries supplied upon request. See package insert accompanying product for a full discussion of warnings, contraindications, complications and prescribing information. Carpentier-Edwards® is a registered trademark of Baxter International Inc.

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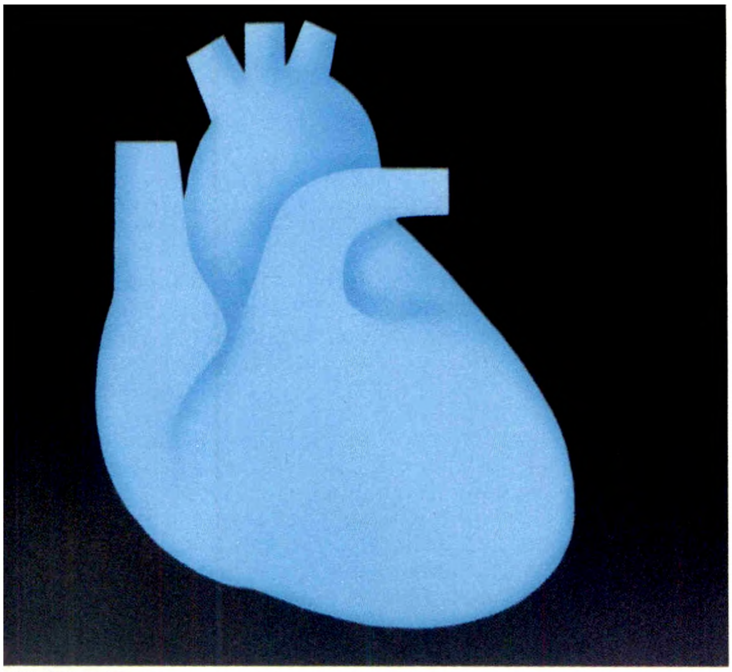

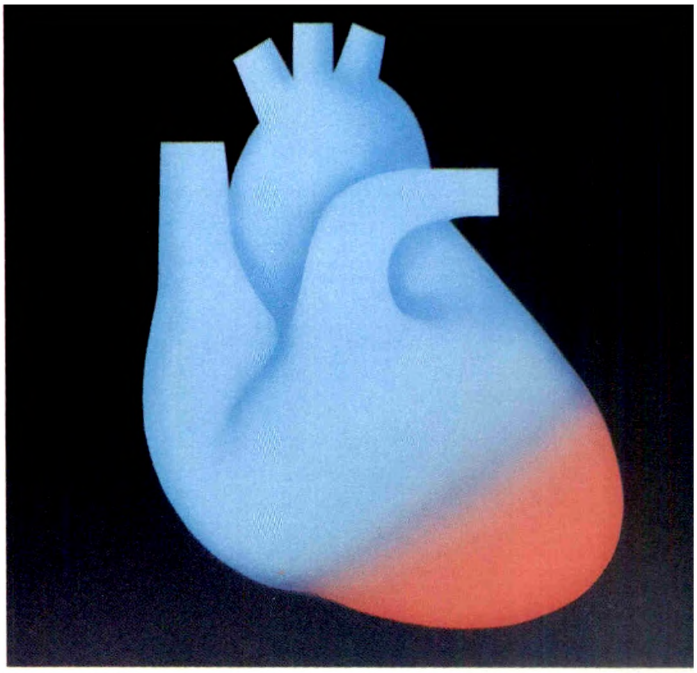

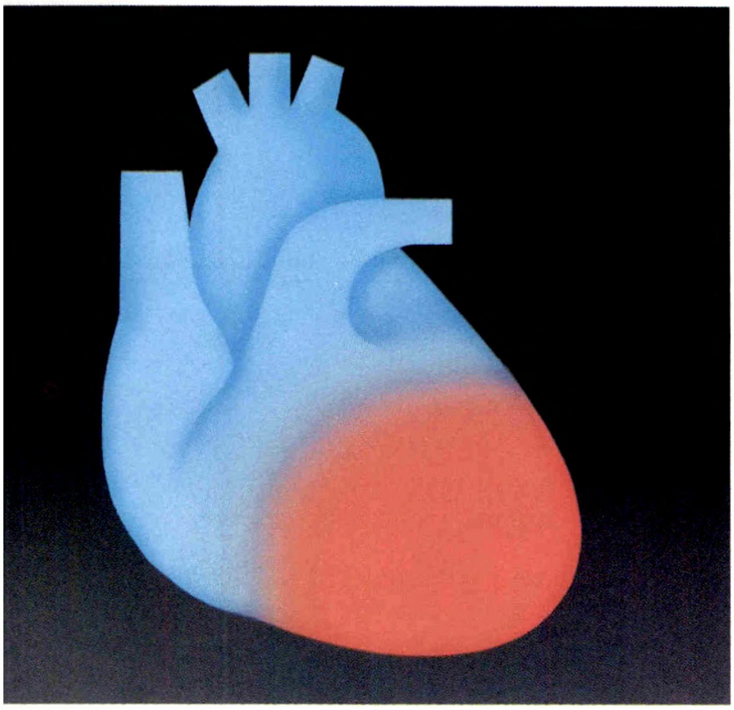

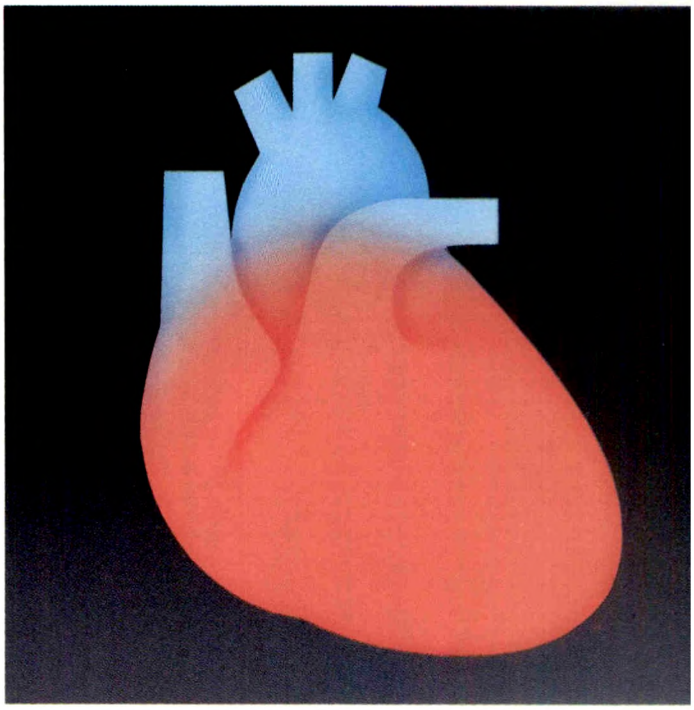

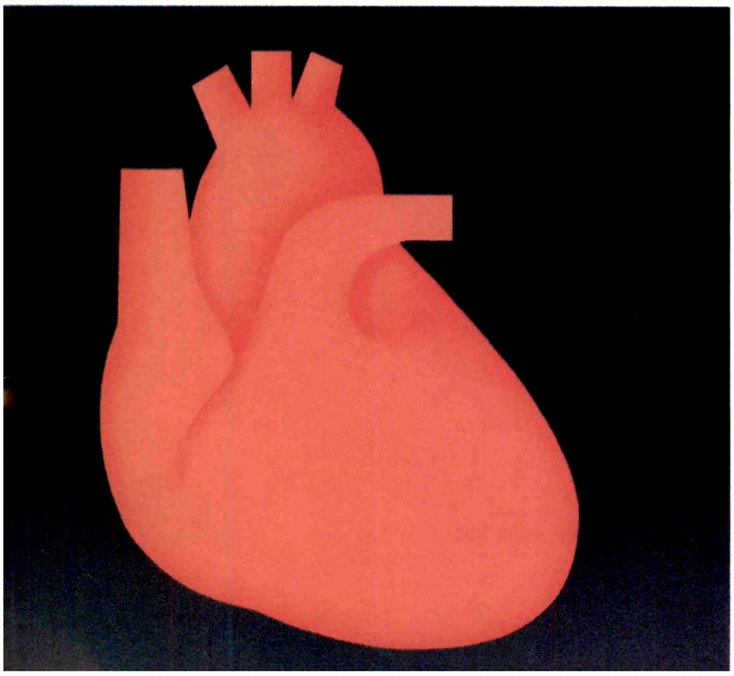

BACK IN THE PINK

In the post-MI heart failure patient, the inotropic action of dobutamine increases tissue perfusion while maintaining a favorable impact on the determinants of myocardial oxygen consumption.

DOBUTREX™
DOBUTAMINE HCl

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See adjacent page for brief summary of prescribing information.

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Dobutrex® Solution
dobutamine hydrochloride injection

Excessive dosages of Dobutrex or other inotropic agents may produce unwanted alterations in blood pressure, heart rate, or ventricular ectopic activity.

Brief Summary. Consult the package literature for prescribing information.

Clinical Pharmacology: Dobutrex Solution is a direct-acting inotropic agent whose primary activity results from stimulation of the ß-receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. n animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol ncrease the cardiac output to a similar degree. In the case of dobutamine, this increase s usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, soproterenol increases the cardiac index primarily by increasing the heart rate while troke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short term—not more than several hours n duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas output returned toward baseline values in others.

The onset of action of Dobutrex Solution is within one to two minutes; however, as much s ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major xcretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The -O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or ricyclic antidepressants does not alter the actions of dobutamine in animals, which ndicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

ndications and Usage: Dobutrex Solution is indicated when parenteral therapy is ecessary for inotropic support in the short-term treatment of adults with cardiac ecompensation due to depressed contractility resulting either from organic heart isease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex Solution.

Contraindications: Dobutrex Solution is contraindicated in patients with idiopathic ypertrophic subaortic stenosis and in patients who have shown previous manifestaions of hypersensitivity to Dobutrex Solution.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex Solution may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Usually, reduction of dosage reverses these effects. Because dobutamine facilitates trioventricular conduction, patients with atrial fibrillation are at risk of developing rapid entricular response. Patients with preexisting hypertension appear to face an ncreased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex Solution may precipitate or exacerbate ventricular ctopic activity, but it rarely has caused ventricular tachycardia.

3. *Hypersensitivity*—Reactions suggestive of hypersensitivity associated with administration of Dobutrex Solution, including skin rash, fever, eosinophilia, and bronhospasm, have been reported occasionally.

4. Dobutrex Solution contains sodium bisulfite, a sulfite that may cause allergic-type eactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivy in the general population is unknown and probably low. Sulfite sensitivity is seen more requently in asthmatic than in nonasthmatic people.

Precautions: 1. During the administration of Dobutrex Solution, as with any adreneric agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex Solution.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex Solution is instituted.

3. Animal studies indicate that dobutamine may be ineffective if the patient has recently received a ß-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex Soluon following myocardial infarction has been insufficient to establish the safety of the rug for this use. There is concern that any agent that increases contractile force and eart rate may increase the size of an infarction by intensifying ischemia, but it is not nown whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed o evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be sed only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex Solution for use in children ave not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex Solution was administered concurrently with other drugs, including igitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosoride dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and cetaminophen. Preliminary studies indicate that the concomitant use of dobutamine nd nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activy*—A 10- to 20-mm increase in systolic blood pressure and an increase in heart rate of to 15 beats/minute have been noted in most patients. (*See* Warnings *regarding exaggerted chronotropic and pressor effects.*) Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Hypotension—Precipitous decreases in blood pressure have occasionally been described in association wth dobutamine therapy. Decreasing the dose or discontinuing he infusion typically results in rapid return of blood pressure to baseline values. In rare ases, however, intervention may be required and reversibility may not be immediate.

Reactions at Sites of Intravenous Infusion—Phlebitis has occasionally been reported. ocal inflammatory changes have been described following inadvertent infiltration.

Miscellaneous Uncommon Effects—The following adverse effects have been reported n 1% to 3% of patients: nausea, headache, anginal pain, nonspecific chest pain, alpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex Solution have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

PA 7235 AMP [050289]

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Clinical Experience With Subxiphoid Drainage of Pericardial Effusions

George M. Palatianos, MD, Richard J. Thurer, MD, Matthew Q. Pompeo, MD, and Gerard A. Kaiser, MD

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To assess the effectiveness of subxiphoid pericardial tube drainage for treatment of pericardial effusion, we reviewed 41 consecutive patients who underwent this procedure during a 14-year period. The patients ranged in age from 7 months to 75 years. All were symptomatic preoperatively. The diagnosis of pericardial effusion was confirmed by echocardiogram in all but 2 patients. Eight patients had acute pericardial tamponade. Subxiphoid pericardial drainage was performed under general (n = 35) or local anesthesia (n = 6). A portion of the anterior pericardium was excised in each patient. There were no perioperative deaths. Thirty-day mortality was 19.5%; there were five late deaths. All deaths were unrelated to pericardial effusion or to the operation. One patient had recurrent effusion requiring pericardiocentesis on the 21st postoperative day. He died five days later of extensive lymphoma. Twenty-eight patients were followed from 1 month to 10 years; mean follow-up was 31.5 months. None developed recurrent effusion or pericardial constriction. We conclude that subxiphoid pericardial drainage is effective for treatment of pericardial effusion.

(Ann Thorac Surg 1989;48:381–5)

Controversy exists concerning the choice of operation for management of pericardial effusion. Traditionally, the surgical approach for a large, persistent, or hemodynamically significant pericardial effusion has been pericardiectomy by left thoracotomy or median sternotomy [1–3]. However, several reports advocate use of the subxiphoid approach for surgical drainage of the pericardium [4–9]. In the present study, we reviewed our experience with subxiphoid pericardial drainage at the University of Miami/Jackson Memorial Medical Center.

Material and Methods

From November 1972 to December 1986 41 consecutive patients (22 female) underwent open subxiphoid pericardial tube drainage for treatment of persistent symptomatic pericardial effusion at the University of Miami/Jackson Memorial Medical Center. This review includes 21 patients reported previously [9]. The patients ranged in age from 7 months to 75 years (mean age, 40.1 years). All were symptomatic preoperatively. Chest pain was present in 16 patients; cough in 11, fever in 12, dyspnea in 25, and weakness in 7. Clinical manifestations included jugular venous distention in 10 patients, pericardial rub in 6, and pulsus paradoxus in 16. Eight patients had hypotension associated with pericardial tamponade. The chest roentgenogram revealed cardiomegaly in 26 patients and was reported as diagnostic of pericardial effusion in 8 patients. The diagnosis of pericardial effusion was confirmed by echocardiogram in 39 patients. Right heart catheterization with a Swan-Ganz catheter was performed preoperatively in 4 patients. Pericardiocentesis was performed preoperatively without complications in 12 patients.

Subxiphoid drainage was performed under general (35 patients) or local anesthesia (6 patients). The procedure has been described previously [9]. A short midline or oblique incision is performed in the epigastrium originating from the xiphoid process or the left sternocostal angle, respectively (Fig 1). The retrosternal prepericardial space is entered by incising the linea alba, excising the xiphoid process, and dissecting retrosternally, or by dissecting cephalad anteriorly to the posterior leaf of the rectus abdominis sheath. Dissection of the prepericardial tissues reveals the lower part of the anterior pericardium. A 3 × 4-cm^2 biopsy specimen is taken under direct vision from the lower aspect of the anterior pericardium. The pericardial cavity is decompressed, and samples of the drained fluid are collected for microbiological cultures and cytological analysis as indicated. The pericardial cavity is digitally explored, presence of tumor or adhesions is assessed, and gentle digital lysis of adhesions and opening of loculations is performed as needed to enhance satisfactory drainage.

For continuous postoperative drainage, two chest tubes are usually inserted in the pericardial cavity through the created defect, exteriorized through separate incisions in the epigastrium, and secured. One tube is usually a 36F right-angle chest tube, which is positioned posteriorly (inferiorly) to the heart with its tip directed leftward. A straight chest tube (usually a 28F) is positioned anteriorly

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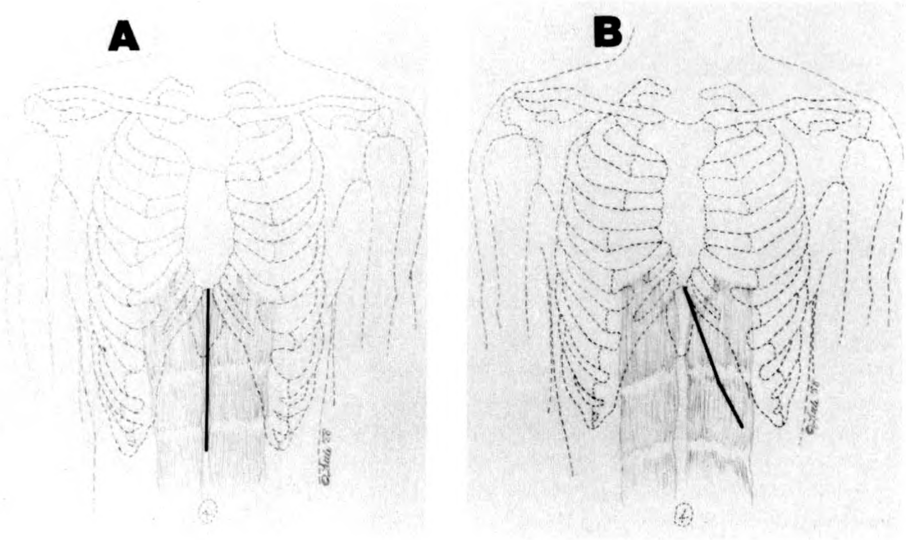

Fig 1. Solid black lines *demonstrate incisions for subxiphoid pericardial drainage: (A) midline; (B) oblique.*

to the heart. The tubes are connected to a system of underwater seal and suction and are removed when fluid drainage ceases.

After hospital discharge, the patients were followed with physical examinations and echocardiograms either in our outpatient clinics or by their private physician.

Results

The cause of the pericardial effusion is shown in Table 1. Of the 14 patients with neoplastic effusion, 13 had effusion of malignant cause. Examination of the resected pericardial segment demonstrated malignancy in 6 patients. Cytological examination of pericardial fluid was positive for malignant cells in 11 patients. In 7 patients with positive cytology, the pericardial biopsy specimen was negative for malignancy, whereas in 2 patients with pericardial biopsy specimens positive for malignancy the cytology of the pericardial fluid was negative for malignant cells. Seven of the patients had lung cancer, 4 had breast cancer, 1 had lymphoma, and 1 had malignant pericardial effusion of undetermined primary source. One patient had pericardial effusion due to sinus histiocytosis.

Microorganisms cultured from pericardial fluid in 7 patients were the following: *Pneumococcus* (2 patients), *Streptococcus viridans* (1 patient), *Hemophilus influenzae* (1 patient), and *Mycobacterium tuberculosis* (2 patients). Yeast grew from purulent pericardial effusion in a 24-year-old intravenous drug abuser who was treated for gunshot wounds to the left hemithorax. However, no identification of a fungus was available in the records. The patient was free of pericardial effusion or constriction 10 years later. In a 9-month-old girl treated for *Hemophilus influenzae* sepsis, purulent pericardial effusion was drained (white blood cell count, 21,700/μL) but grew no microorganism.

Table 1. Cause of Pericardial Infusion

Cause of Effusion	No. of Patients
Idiopathic	9
Neoplastic	14
Uremic	9
Purulent	6
Tuberculous	2
Dressler syndrome	1[a]
Total	41

[a] Two months after acute myocardial infarction.

There were no perioperative deaths. Thirty-day mortality was 19.5% (8 patients). Four patients had malignant pericardial effusion and died of extensive malignancy 20 to 27 days postoperatively. Two other patients had tuberculous pericarditis and died of acquired immunodeficiency syndrome 16 and 30 days postoperatively. Acid-fast bacilli were cultured from pericardial fluid in both of these latter patients. However, granulomas were not present in the pericardium. The remaining 2 patients had uremic pericardial effusion; 1 of them died of pneumonia on the 30th postoperative day, and the other suffered cardiac arrest and died intraoperatively during revision of clotted arteriovenous shunt five days after pericardial drainage.

Recurrent pericardial effusion occurred in 1 patient with terminal malignant disease due to extensive lymphoma with pericardial involvement. The effusion was drained by pericardiocentesis on the 21st postoperative day. The patient died of his malignancy five days later without evidence of recurrence of the pericardial effusion. No other patients who died had evidence of clinically significant pericardial effusion or constriction, and their deaths were not related to the pericardium or to the operation. There were no other major postoperative complications. Transient ventricular arrhythmias occurred in 2 patients in the early postoperative period but were controlled with lidocaine and did not persist for more than a day.

Three patients were lost to follow-up immediately after hospital discharge. One of them was treated for uremic

Table 2. Cause of Pericarditis and Follow-up in 28 Patients

Cause of Pericarditis	No. of Patients	Follow-up (mo) Mean	Follow-up (mo) Range
Idiopathic	8	30.4	1.5–76.3
Malignant	6	6.8	1.5–16.5
Sinus histiocytosis	1	17.3	. . .
Uremic	6	17.8	1–34
Purulent	6	61.3	1–120
Dressler syndrome	1	105.3	. . .
Total	28	31.5	1–120

pericarditis; the other 2 were treated for malignant pericardial effusion. Two additional patients treated for idiopathic or malignant pericardial effusion were lost to follow-up 20 days and 14 days, respectively, after hospital discharge. Twenty-eight patients were followed from 1 month to 10 years (Table 2). Five patients had follow-up of 1 (n = 2) or 1.5 months (n = 3). These patients were treated for idiopathic (n = 2), uremic (n = 1), purulent (n = 1), or malignant pericardial effusion (n = 1). Mean follow-up was 31.5 months. None of these patients developed recurrence of pericardial effusion necessitating pericardiocentesis or repeat surgical drainage. Postoperative M-mode and two-dimensional echocardiography was performed in 13 patients (46.4%) and confirmed the absence of recurrent effusion. Late death occurred in 7 patients. Five had metastatic malignancy and died of their disease 2 to 16.5 months postoperatively. Another patient, who had been operated on for idiopathic pericardial effusion, died of bilateral pneumonia 29 months later, and another with end-stage renal failure died of acute myocardial infarction 31 months after subxiphoid drainage. Of the 10 patients with malignant pericardial effusions and complete follow-up, 8 died 20 days to 16.5 months postoperatively. The remaining 2 patients were alive 4 and 7.5 months postoperatively.

Comment

Pericardiectomy by left thoracotomy or median sternotomy has been considered the procedure of choice for patients with pericardial tamponade or persistent large pericardial effusions [1–3]. Several reports suggest that the less invasive subxiphoid approach to the pericardial cavity is an effective and perhaps preferable alternative [4–9].

The noted French surgeon Baron Dominique-Jean Larrey (1766–1842) was probably the first to use the subxiphoid approach for drainage of the pericardial cavity in 1824. His experience is described in detail in his *Clinique Chirurgicale,* in which the first description of the subxiphoid approach to the pericardium is outlined [10]. Larrey advocated use of the subxiphoid approach to the pericardium, considering this an easy operation with small risk, offering the most chances of success because (1) at this dependent point where the pericardial opening is made the collection of fluid is more prominent and the pericardium is at a distance from the heart, (2) there is easy drainage of the fluid without disturbance of heart function, and (3) formation of adhesions may be limited to the inferior aspect of the heart and spare the remaining pericardium [10].

The subxiphoid approach to the pericardium can be achieved by a midline or an oblique incision (Fig 1). The oblique incision was advocated by Larrey [10]. We believe that the oblique incision is preferable in patients with a wide sternocostal angle. In patients with a narrow sternocostal angle, the midline incision with resection of the xiphoid process is preferred.

Use of the subxiphoid approach to the pericardium was popularized by Willius and Dry [11], Cassell and Cullum [12], Schlein and colleagues [13], and Fontenelle and associates [14]. Several investigators consider subxiphoid pericardial tube drainage an effective procedure for patients with uremic [6], malignant [15–17], traumatic [18], purulent [6], and even tuberculous pericardial effusion [6].

The average recurrence rate of the effusion after subxiphoid tube pericardial drainage is 4.9% in the 513 patients reported (Table 3). In our experience, 1 patient (2.4%) with extensive lymphoma with pericardial involvement had recurrence of clinically significant pericardial effusion after subxiphoid drainage. No clinically significant effusion was present five days later when he died of his malignancy.

Pericardiectomy, partial or extensive, is the traditional approach for surgical management of uremic pericardial effusion, often in association with pericardiocentesis [23–25]. In patients with uremic pericardial effusions and evidence of hemodynamic compromise (pulsus paradoxus or pericardial tamponade), or large pericardial effusions resistant to intensive hemodialysis, we advocate use of the subxiphoid approach as initial surgical management. The low operative mortality and small recurrence rate make the subxiphoid approach the procedure of choice for initial surgical drainage. A more extensive pericardiectomy can be performed later if necessary. In our experience, however, recurrence of the effusion necessitating reoperation did not occur. In patients with marked hemodynamic compromise due to pericardial tamponade, pericardiocentesis may be attempted with a 7F pigtailed catheter, preferably guided by two-dimensional echocardiography [26]. Intrapericardial injection of steroids has been advocated in an effort to limit recurrence of effusion [27, 28].

Subxiphoid tube drainage of pericardium is successful in cases of malignant pericardial effusion [15–17]. Thoracotomy provides better exposure of the pericardium and allows easier release of adhesions than the subxiphoid approach [29]. However, thoracotomy itself poses a higher operative risk, especially in patients with malignant pericardial effusions, whose condition is often markedly compromised [29]. We believe that in these cases the less invasive subxiphoid approach effectively drains the pericardium and is preferable. In addition, the subxiphoid approach can be effectively performed under local anesthesia, reducing the surgical risk in severely ill patients [4,

Table 3. Rate of Effusion Recurrence and Constriction After Subxiphoid Tube Pericardial Drainage

Reference	No. of Patients	Recurrence[a]	Constriction[a]
Schlein et al [13]	7	1	0
Fontenelle et al [14]	12	0	0
Lajos et al [4]	22	0	1
Santos and Frater [5]	46	2	0
Hankins et al [15]	13	0	1
Alcan et al [19]	18	1	0
Levin and Aaron [20]	28	2	1
Prager et al [6]	25	0	0
Berman et al [16]	3	0	0
Little et al [7]	32	0	0
Piehler et al [21]	13	2	3
Reitknecht et al [17]	46	2	0
Ghosh et al [8]	108	5	0
Mills et al [22]	99	9	0
Palatianos et al (present series)	41	1	0
Total	513	25 (4.9%)	6 (1.2%)

[a] Number of patients who developed clinically significant recurrent effusion or pericardial constriction postoperatively.

5, 8, 12–20]. Breast and lung carcinomas and lymphomas are the most common malignancies that metastasize to the pericardium and produce pericardial effusion [30]. In our experience, 7 of 13 patients with malignant pericardial effusion had lung cancer, 4 had breast cancer, 1 had extensive lymphoma, and 1 had malignant pericardial effusion proven by positive cytological studies but with an undetermined primary site. Four patients died of their malignancy within the first postoperative month, whereas 2 others were alive at 4 and 7.5 months postoperatively without recurrence of the effusion.

In patients with infectious pericarditis, which is usually associated with generalized sepsis, use of the less invasive subxiphoid approach effectively drains the pericardial cavity and avoids contamination of the pleural space [6]. Grossly purulent pericardial effusions were drained from 6 of the patients. A microorganism was cultured in 5 of them. However, the data available on 1 patient from whom yeast was cultured cannot exclude the possibility that the yeast was a contaminant. In another patient, a grossly purulent pericardial effusion grew no microorganism. This was a 9-month-old girl who was receiving antibiotics for *Hemophilus influenzae* sepsis, which could have resulted in sterilization of the pericardial effusion. The two patients with tuberculous pericarditis had acquired immunodeficiency syndrome, and despite adequate drainage of the pericardium and antituberculous treatment they died 16 and 30 days postoperatively without evidence of recurrence. The remaining patients with purulent pericarditis did well, with resolution of the infection and no evidence of pericardial effusion after a mean follow-up of 5.1 years (Table 2).

One reason for avoiding limited pericardial resection is the possibility of postoperative occurrence of pericardial constriction. The incidence of pericardial constriction developing after subxiphoid surgical drainage of pericardial effusions is 1.2% (Table 3). Constrictive pericarditis after subxiphoid pericardial drainage developed in 1 patient in the experience of Lajos and associates [4] and in 1 patient in the report by Levin and Aaron [20]. The patients were suffering of pyogenic and uremic pericarditis, respectively; both were treated successfully with total pericardiectomy [4, 20]. Piehler and associates [21] reported 3 patients in whom pericardial constriction developed within 5 months of subxiphoid pericardial drainage. However, 2 of them had subxiphoid drainage for management of radiation-induced pericardial effusion, and 1 had drainage for management of malignant pericarditis that resulted in carcinomatosis [21]. Hankins and colleagues [15] also reported a patient who developed pericardial constriction 5 months after subxiphoid pericardial drainage. This patient had received chest wall irradiation for treatment of breast carcinoma.

Radiation-induced pericardial effusion occurs in 30% of patients who receive 4,000 rads or more of mediastinal irradiation for treatment of lymphoma or other radiosensitive neoplastic conditions. In about 42% of these patients the effusion is persistent and may require surgical drainage [31]. Prolonged survival is anticipated for such patients, in whom the irradiation-affected pericardium will probably continue to produce the effusion. Therefore, extensive pericardiectomy rather than subxiphoid drainage is recommended for surgical management of radiation-induced pericardial effusion [9, 32].

Subxiphoid tube drainage of the pericardium is effective for initial surgical management of large, persistent, and hemodynamically significant pericardial effusions of uremic, neoplastic, purulent, or idiopathic etiology. It is particularly indicated for pericardial effusions of any cause in compromised patients as it is an effective, less traumatic, and therefore preferable alternative to extensive pericardiectomy. In cases of radiation-induced pericardial effusion, extensive pericardiectomy is the recommended surgical approach.

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Surgical Closure of the Patent Ductus Arteriosus in the Neonatal Intensive Care Unit

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Efficacy of surgical closure versus indomethacin for treatment of patent ductus arteriosus in symptomatic neonates is an ongoing controversy. In recent years, surgical closure has been performed in the neonatal intensive care unit rather than the operating room in some centers, creating further controversy. In a retrospective study of the charts of 115 sequential patent ductus arteriosus surgical closures performed in the neonatal intensive care unit in premature infants, we found no surgical morbidity or mortality. Ninety-nine of these infants of less than 33 weeks gestational age were evaluated for various factors that might influence outcome. All were operated on within 72 hours of diagnosis, with an extrapleural approach and metal clips used for closure of the ductus. All infants were extubated at an average of 33 weeks in each age group studied unless they had underlying severe bronchopulmonary dysplasia. We conclude that surgical closure of the symptomatic patent ductus arteriosus in neonates is safe and 100% effective, with none of the reported complications of indomethacin therapy, and should be the treatment of choice in neonates aged less than 33 weeks (gestational age) at birth with symptomatic patent ductus arteriosus. Closure performed in the neonatal intensive care unit eliminates transport risks and is ultimately safer and easier than transport to an operating room.

(Ann Thorac Surg 1989;48:386–9)

Surgical versus pharmacological closure of the patent ductus arteriosus (PDA) in neonates remains an area of avid debate. Surgical closure has been reported to result in earlier ventilator weaning by Cotton and colleagues [1], but Bhat and co-workers [2] reported that ventilator weaning tended to occur at 33 weeks of conceptional age with medical treatment or early or late surgical closure. Surgical closure performed in the neonatal intensive care unit (NICU) has also been advocated by some investigators. We report a large series of surgical closures in neonates with symptomatic PDA, focusing specific attention on the safety and efficacy of operation in the NICU and time of ventilator weaning in various subgroups classified by gestational age (GA) at birth.

Material and Methods

From July 1984 to December 1987, 115 premature infants underwent surgical closure for symptomatic PDA in the NICU at Iowa Methodist Medical Center with no operation-related deaths or morbidity. All 115 records were reviewed for various factors that might influence patient outcome. Ten patients were still hospitalized and thus had incomplete charts and could not be entered into the study. Six infants of more than 33 weeks GA at birth were not included; thus, 99 patients comprised the study group. Diagnosis was established by the clinical findings of a hyperdynamic precordium, bounding peripheral pulses, worsening respiratory status, and radiographic evidence of pulmonary edema and cardiomegaly, and was confirmed by color-flow Doppler and two-dimensional echocardiogram in every case. Because indomethacin is generally not used in infants aged less than 33 weeks GA by our neonatologists, nearly every infant with a symptomatic PDA in this time period underwent surgical closure. All patients had respiratory distress syndrome and required mechanical ventilation both preoperatively and postoperatively.

Operation was performed in a small operating room immediately adjacent to the NICU. The infants were transported the short distance to the operating room in an incubator and then transferred to the operating room table. Fentanyl and pancuronium were used as anesthesic agents in 81 (82%) patients, ketamine or ketamine and pancuronium was used in 13 (13%), and atracrium besylate and ketamine or morphine were used in 5 (5%). An extrapleural surgical approach was used through a small left posterolateral thoracotomy incision of the fourth intercostal space. After the ductus was closed slowly with a pair of forceps to assess the change in blood pressure, two hemoclips were placed adjacent to the aorta while the recurrent laryngeal nerve was pushed carefully out of the way medially. No chest tubes were placed. The lungs were manually inflated, and the ribs were reapproximated with a single 0-Tevdek suture. The muscle was closed with 3-0 Vicryl and the skin with 4-0 Vicryl and Steri-strips. Total operating time was generally less than 15 minutes. The infants were then transferred back to the NICU for continued medical management.

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Table 1. Characteristics of 99 Infants Operated on for Patent Ductus Arteriosus

Variable	Group 1	Group 2	Group 3	Total
No. of patients	18	52	29	99
Male/female ratio	11:7	28:24	15:14	54:45
Gestational age (wk)				
Range	23–26.5	27–29.5	30–32	
Mean	24.9	28.2	30.8	28.36
Weight (g)				
Range	480–1,300	650–1,560	1,000–2,155	
Mean	809	1,102	1,414	1,140
Twins	5 (28%)	13 (25%)	5 (17%)	23%

Results

The 99 patients who were sequentially operated on were divided into three groups based on GA (determined by dates and ultrasound). Group 1 consisted of 18 patients of less than 27 weeks GA (range, 23 to 26.5 weeks; weight range, 480 to 1,300 g). There were 11 boys and 7 girls, including 5 twins. There were no hospital deaths in this group. Four patients were transferred to other tertiary centers for long-term care of ventilator-dependent bronchopulmonary dysplasia (Table 1).

Group 2 consisted of 52 patients of at least 27 weeks and less than 30 weeks GA (range, 27 weeks to 29.5 weeks; weight range, 650 to 1,560 g). There were 28 boys and 24 girls, including 13 twins. There were two hospital deaths in this group resulting from complications of prematurity, and 5 infants were never weaned from the ventilator during hospitalization because of severe bronchopulmonary dysplasia or laryngomalacia.

Group 3 consisted of 29 patients of at least 30 weeks and less than 33 weeks GA (weight range, 1,000 to 2,155 g). There were 15 boys and 14 girls, including 5 twins. There was one hospital death in this group resulting from complications of prematurity. Three infants were not weaned from the ventilator or were transferred.

Overall, there were no operation-related deaths. Three patients who died and the 12 who were not weaned from the ventilator or were transferred to other hospitals were not included in the calculation of time from operation to ventilator weaning (Table 2). Most infants were operated on between 36 and 72 hours after the diagnosis of symptomatic PDA was made (Table 3). The average age at ventilator weaning was approximately 33 weeks from conception in all groups (Table 2; Fig 1). The number of days from operation to weaning from total parenteral nutrition and starting complete oral sustenance appeared to be related to GA at birth, with group 1 taking much longer than group 3 (16.7 versus 4.8 days). Bronchopulmonary dysplasia occurred in 12% and 17% of patients in groups 2 and 3, respectively, but in 50% of group 1 infants. Necrotizing enterocolitis occurred in 7% overall. Change in blood pressure ranged from 0 to 27 mm Hg with closures. No complications were directly related to operation. One infant had prolonged hypotonia from the anesthetic agent Tracrium.

Table 2. Ventilator Weaning in 84 of 99 Infants After Operation for Patent Ductus Arteriosus[a]

Variable	Group 1	Group 2	Group 3	All
No. of patients	14	45	25	84
Days to ventilator weaning	49.9	25.2	9.1	24.97
Gestational age at ventilator weaning (days)	32.8	32.9	33.2	32.97

[a] Three infants who died and 12 who were transferred to other hospitals were not included in these calculations.

Table 3. Results and Complications

Variable	Group 1	Group 2	Group 3	All
Age at diagnosis (days)	5.0	4.9	5.2	5.0
Age at operation (days)	6.3	7.2	7.5	7.12
Days to total parenteral nutrition weaning	16.7	9.9	4.8	9.6
Bronchopulmonary dysplasia	9 (50%)	6 (12%)	5 (17%)	19%
Necrotizing enterocolitis	1 (5%)	5 (9.6%)	1 (3%)	7%

Comment

Surgical closure of the PDA in symptomatic neonates has been clearly shown to decrease morbidity and mortality in the disorder [3–5]. Medical management alone using fluid restriction, diuretic agents, digoxin, and transfusion results in a prolonged course of total parenteral nutrition and intravenous fluid restriction and more pronounced ventilator requirements.

Indomethacin for closure has been advocated as, or shown to be, effective for infants of more than 34 weeks GA or with a weight of 1,500 g who have symptomatic PDA [6–8], but researchers have also recommended its routine use in symptomatic neonates of less than 34 weeks GA, with medical management alone being re-

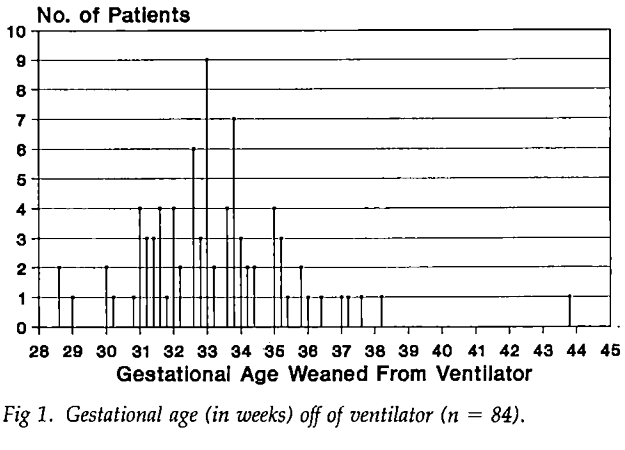

Fig 1. Gestational age (in weeks) off of ventilator (n = 84).

served for those of more than 34 weeks GA [9, 10]. Potential complications of indomethacin include renal dysfunction, hyperbilirubinemia, clotting abnormalities, gastrointestinal bleeding [11–16], and failure of treatment in up to 42% [6, 17–19]. It is particularly ineffective in smaller infants [20] and is definitely contraindicated in patients with renal insufficiency, thrombocytopenia, coagulopathies, jaundice, necrotizing enterocolitis, and intraventricular hemorrhage; up to 38% of potential patients have contraindications to its use [18]. Indomethacin treatment may delay surgical treatment, having a detrimental effect on prognosis in patients weighing less than 1,500 g with severe respiratory distress syndrome [8] and possibly resulting in a longer period of ventilator support [21].

Because surgical closure can be safely accomplished in neonates of any GA with little morbidity and essentially no surgical mortality [6–8, 22, 23] and has the added advantage of instant, reliable 100% ductus closure, it has become the procedure of choice in our institution. Nutritional and fluid management of the infants is subsequently easier.

Surgical closure in the NICU has been recently advocated because of the decreased risk of hypothermia or interruption of vascular access, monitoring equipment, or the endotracheal tube [7, 22, 24]. It is relatively easier to move the operating room personnel and anesthesia equipment to the NICU than to transport the neonate with all its paraphernalia to the operating room. Our patients were treated in a specially equipped operating room adjacent to the NICU: it is easier to perform the operation in the NICU with the infant in its own isolette without having to move it at all, as we have done since reviewing this series of patients. The goal is to eliminate risks associated with transport of these fragile human beings.

We believe the best surgical approach is extrapleural. It is quick and easy, does not require postprocedure chest tube placement, and has been shown to decrease morbidity [25]. Application of one or two metal clips near the aorta reduces the risk of recurrent laryngeal nerve injury and does not require complete mobilization of the ductus, thus theoretically reducing the risk of excessive bleeding. Fentanyl and pancuronium appear to be safe anesthesic agents.

Cotton and colleagues [1] demonstrated earlier ventilator weaning in infants weighing less than 1,500 g with asymptomatic PDA treated by early surgical closure [1]. Bhat and co-workers [2] showed that infants treated with medical management alone, early surgical closure, and late surgical closure were all extubated at about 33 weeks of conceptional age. All of our patients underwent early surgical closure; the 84 who were weaned from the ventilator were extubated at approximately 33 weeks conceptional age (see Table 2), in agreement with the findings of Bhat and co-workers. Prolonged ventilation times are believed to increase the risk of bronchopulmonary dysplasia [26]. Group 1 patients required an average of 49.9 days of mechanical ventilation compared with 25.2 and 9.1 days for patients in groups 2 and 3. Bronchopulmonary dysplasia occurred in 50% of group 1 patients and only 12% and 17% of patients in groups 2 and 3. This reflects the severity of the underlying pulmonary disease and the extended ventilation time in group 1 patients. The incidence of bronchopulmonary dysplasia will probably always be high in infants with symptomatic PDA of less than 27 weeks GA because of the immaturity of the lungs and the need for ventilator support to 33 weeks of conceptional age. The need for positive end-expiratory pressure and high oxygen levels in this group can only contribute to permanent lung injury.

All groups were weaned fairly quickly from total parenteral nutrition to an enteral diet (4.8 to 16.7 days), but this is an independent factor as we have no group with which to compare the patients in this retrospective study. The incidence of necrotizing enterocolitis was fairly uniform throughout the groups and appears to be consistent with reported rates in both surgically and indomethacin-treated groups [6–8].

In conclusion, surgical closure of a symptomatic PDA in the neonate has many advantages and none of the disadvantages of indomethacin treatment. It is safe and instantly effective and allows easier management of fluids, nutrition, and ventilator support postoperatively. The operation can be performed safely and efficiently in the NICU using operating room personnel, eliminating the risks of transport to the infant. Age at operation appears to have no effect on the time of ventilator weaning and extubation; all infants tend to be ready for extubation at 33 weeks of conceptional age regardless of GA at birth. Those of lesser GA are at increased risk for development of bronchopulmonary dysplasia. Institution of tube feeding can occur shortly after operation when fluid status has stabilized, with gradual progression to complete enteral feeding.

Addendum

From January 1988 to January 1989, 27 additional patients have been operated on with no morbidity or deaths related to the operation.

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FDA Recalls: How Do Pacemaker Manufacturers Compare?

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To evaluate an apparent perception that there is no difference in reliability among the products of the major cardiac pacing system manufacturers, an extensive review of US Food and Drug Administration regulatory actions was performed. The study period was July 1974 through June 1987. The total number of affected devices was collected for each manufacturer. Available sales data were used to calculate their percentage of recalled products during two time periods. The percentage of potentially high-risk devices (Food and Drug Administration class I and II recalls) was high for one company, moderate for one, and relatively low for the rest. Potential biases in some other sources of reliability information, as well as implications for regulatory policies, are discussed. The data reported establish that there have been past deficiencies in recall management. Although further pacing device recalls are probable, appropriate early regulatory and manufacturer action should help to assure that both the immense cost and patient distress caused by pacer and related product problems in the past can be minimized in the future.

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Most physicians involved in cardiac pacing believe that reliability is of paramount importance in device selection. At the same time, few functional or reliability differences are generally perceived to exist among the products of different pacemaker manufacturers [1–3]. To determine the correctness of this assumption, a review was undertaken of US Food and Drug Administration (FDA) actions affecting the products of the seven manufacturers whose devices account for the majority of North American implants [1].

Material and Methods

Food and Drug Administration actions were collected according to recall classification, device, manufacturer, and year. Although FDA recall definitions [4] have remained relatively constant over the survey years (Appendix), consideration of actions not formally classified as recalls has varied. Originally, most unclassified actions were designated as Advisories, but beginning in 1984 the term *Medical Device Safety Alert* was introduced for voluntary communications from manufacturers and related organizations. Because the present Safety Alert definition includes "risk of substantial harm," there is some overlap with class I and II recall definitions. Although not used to date, unclassified actions initiated at the request of the FDA are now termed *Medical Device Notifications*. For this report, all Advisories and Safety Alerts have been combined into a single category.

The source of the recall data was FDA records, including *FDA Enforcement Reports* and the *Summary Report of Pacemaker and Lead Recall Statistics* obtained through provisions of the US Freedom of Information Act [5, 6]. Each implantable rhythm control system consists of a pulse generator and one or more electrodes. Because of the integral role of accessory equipment such as programmers and the tendency or necessity to use components from the same manufacturer together, each implant was considered a multicomponent system. Patient risk can stem from malfunction of any of the pacing system components.

Recall data were collected for the 13-year period between July 1974 and June 1987. The year 1974 was chosen as the beginning of the study because few of the products that led to major recalls were in distribution before that time. In addition, Cardiac Pacemakers Inc, Intermedics, and Pacesetter, which together supplied one third of the pacemakers implanted in North America during the study period, began substantial distribution of their products during this period. This was also the beginning date of *Performance of Implantable Cardiac Rhythm Management Devices* [7], a multicenter study that regularly reports annual survival rates for selected models of implantable devices for most of the major pacemaker manufacturers and is widely quoted.

To allow normalized comparison between manufacturers, unit sales data were collected from independent commercial sources [8–13]. Sales estimates for the United States are available for five companies for the entire 13-year period, and worldwide sales estimates are available since 1980 for six of the seven manufacturers having a major role in North American pacing. Comparisons were limited to FDA class I and II recalls as, by definition, these products are associated with potentially serious adverse health consequences for recipient patients.

Although Advisories and Alerts may encompass trivial to life-threatening problems, no attempt has been made to subclassify the more serious occurrences or to include them in the comparative data. Similarly, more accurately

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Table 1. Devices Subjected to FDA Classified Recalls and Advisories by Class: July 1974 Through June 1987

Class	Cordis[a]	Medtronic	Cardiac Pacemakers Inc	Telectronics	Intermedics	Biotronik	Pacesetter
A: Implantable cardiac pulse generators							
I	52,664	0	1,693	3,727[b]	0	1,050	690
II	7,629	25,344[c]	1,511[d]	50	1,547	0	8
III	5	0	0	0	0	0	0
Advisory, Safety Alert	33,270[e]	21,517	19,000	11,013[f]	3,698	419	0
Total pulse generators	93,568	46,861	22,204	14,790	5,245	1,469	698
B: Leads							
I	0	26,761[g]	0	0	0	0	0
II	83	0	0	0	207	0	0
III	20	0	0	0	0	0	0
Advisory, Safety Alert	0	17,900[h]	0	0	0	0	0
Total leads	103	44,661	0	0	207	0	0
C: Programmers							
I	0	0	0	0	0	0	0
II	4,370	6,450	0	0	0	0	0
III	0	174	0	0	1,099	0	0
Advisory, Safety Alert	5,046	0	0	0	0	0	0
Total programmers	9,416	6,624	0	0	1,099	0	0
Total all categories	103,087	98,146	22,204	14,790	6,551	1,469	698
Total classes I and II	64,746	58,555	3,204	3,777	1,754	1,050	698

[a] Companies listed in order of total devices classified by FDA.

[b] The FDA class I Telectronics Optima-MPT models 5281 and 5282 recall of June 3, 1987, does not include any estimate of the number of units implanted outside the US even though international distribution is noted. The number of units at risk worldwide was 9,272, including the 3,727 in the US (see Table 1), 4,805 in Europe, and 740 elsewhere [14].

[c] Not including the November 7, 1984, class II recall of Medtronic Versatrax and Byrel SX units distributed outside the US, as no estimate of numbers involved is provided in the FDA report.

[d] Not including any devices from the April 14, 1982, class II recall of Cardiac Pacemakers Inc Microthin DIs, PIs, DIIs, and PIIs. No estimate of the number of units is provided in FDA reports, although the serial numbers listed indicate that several thousand pacers were involved.

[e] Not including the June 24, 1987, extension of the Cordis Sequicor II, Sequicor III, Gemini Theta, and Gemini III Safety Alert to include additional serial numbers, as the number of units is not given in the FDA report.

[f] Not including the January 7, 1987, extension of the Telectronics Autima Safety Alert to include all serial numbers and codes, as no estimate of the additional number of units involved is provided in FDA reports.

[g] Not including the June 25, 1980, class I recall of 2,877 Medtronic Temptron pacing leads distributed to Australia, Canada, Hong Kong, Japan, the US, and Venezuela, as they did not form part of a permanent implantable system. Not including the initial class I recall of Medtronic bipolar model 6,972 leads distributed to Canada and at least six other countries outside the US, as no estimate of the number of additional leads is provided in the FDA reports of March 14 and June 27, 1984. The number of devices at risk worldwide at that stage was more than 29,807: 26,761 in the US (see Table 1) and 3,046 in Europe [15]. Not including the July 25, 1984, extension of the class I recall of the Medtronic bipolar model 6972 lead to include all devices manufactured between December 1979 and February 1982, as no estimate of the additional numbers involved is provided in the FDA report. Before this extension, the 6972 recall had been limited to leads with serial numbers followed by the suffix "R" and suffix "V" leads with serial numbers lower than ND 0034059V [15]. Not including reports of involvement of all Medtronic 6972 leads, including those manufactured after 1982. Sales continued into 1984. The number of bipolar 6972 leads at risk approximates 50,000, with an FDA estimated 20% failure rate by 3 years [16].

[h] Not including extension of the Safety Alert initially covering approximately 14,000 Medtronic bipolar 4002 Ring Tip leads to include more than 18,000 US implants and 40 leads implanted in Spain and Norway [17].

This table also does not include 16,210 Cordis and Medtronic lead introducer kits distributed in Canada, Europe, South America, and the US subject to class II recall in 1981, as these devices did not form part of a permanent implantable system.

defined numerical data on problem devices available from sources other than the FDA were not included in the calculations of comparative risks but are included for completeness in the footnotes to Table 1. Restricting comparisons to only FDA data was considered the most reliable approach, as other sources of information may not be equivalently available for all pacing products.

Results

Table 1 summarizes all pacemaker and related-device FDA actions by class for the 13-year study period and shows the totals for each manufacturer for all categories. The companies are listed in order from left to right, with the one having the highest number of actions first, the lowest last. The order remains essentially the same when class I and II actions are considered separately. Furthermore, although the total number of recalled devices would increase for each of the four companies with the highest number of recalls if the data in the footnotes were added, the order again would not change.

Table 2 summarizes all pacemaker and related-device FDA actions by year and manufacturer. Almost 250,000 devices were recalled during the period reviewed, with quite dramatic year-to-year variations for several of the companies, as shown graphically by the cumulative totals in Fig 1. Cordis had substantial recalls during 1975 and 1976 and then had 7 essentially trouble-free years before

Table 2. Number of Devices Subjected to FDA Classified Recalls and Advisories by Year: July 1974 Through June 1987

Year	Total	Cordis	Medtronic	Cardiac Pacemakers Inc	Telectronics	Intermedics	Biotronik	Pacesetter
1974	1,333	283	0	0	0	0	1050	0
1975	17,641	17,638	3	0	0	0	0	0
1976	22,574	1,222	20,452	0	0	900	0	0
1977	1,548	0	1,100	0	0	448	0	0
1978	738	0	0	738	0	0	0	0
1979	121	0	0	0	0	113	0	8
1980	39,020	20	20,000	19,000	0	0	0	0
1981	3,750	8	44	0	0	3,698	0	0
1982	522	0	427	9	0	86	0	0
1983	3,245	0	3.000	245	0	0	0	0
1984	42,364	10,548	30.123	1,693	0	0	0	0
1985	43,891	41,259	1.473	0	50	0	419	690
1986	46,672	30,903	3.624	0	10,839	1,306	0	0
1987	23,526	1,206	17.900	519	3,901	0	0	0
Total	246,945	103,087	98.146	22,204	14,790	6,551	1,469	698

major problems recurred between 1984 and 1987. All other manufacturers, with the exception of Biotronik, began with very low rates of recall, but problems occurred early and relatively frequently for Medtronic and sporadically for the other companies. Telectronics' pattern is unique, with no recalls from 1974 through 1984, followed by 2 bad years in 1986 and 1987. This was not related to Telectronics absorption of Cordis; because where amalgamations occurred products remained assigned to the original manufacturer.

Table 3 relates class I and II recalls for July 1980 through June 1987 to worldwide unit sales for 1980 through 1986 inclusive. Data for this period were available for six of seven manufacturers. The percentage of affected implants was determined, except for Biotronik, for which independent estimates of sales were not obtained. Thus, a normalized comparison of recall rates is provided for most North American pacer implants for the first 7 years of the current decade.

Table 4 relates 13-year class I and II recalls to US unit sales during 1974 through 1986 inclusive for companies for which sales data were available. A recall percentage was calculated for each manufacturer. Comparative data cannot be provided for Telectronics and Biotronic, but for the other five manufacturers the pattern of Table 3 is confirmed (ie, one company had a very high FDA recall

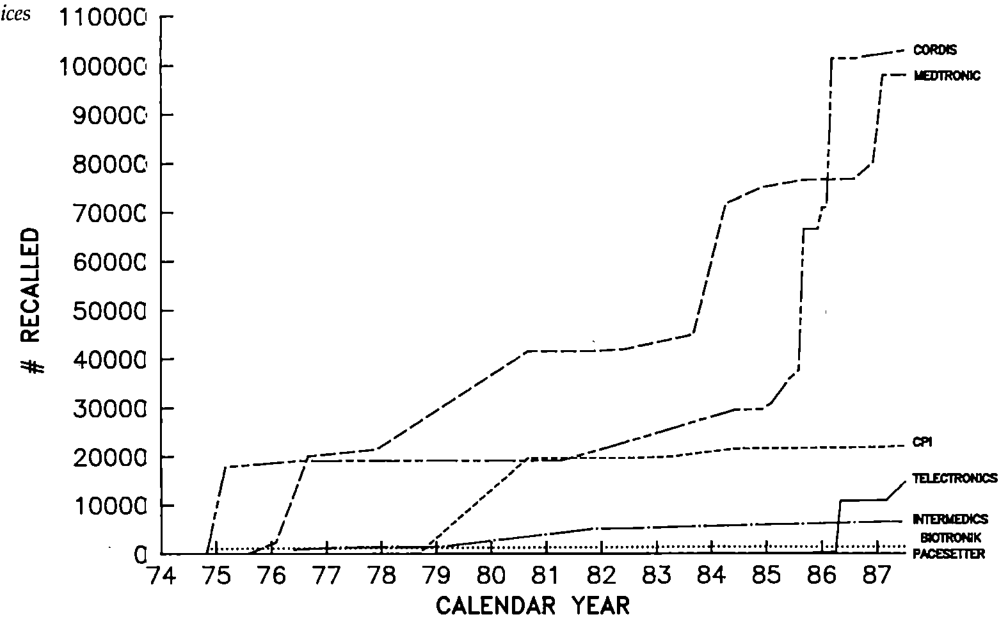

Fig 1. Cumulative number of devices recalled for the manufacturers included in this report.

Table 3. Devices Subjected to Class I and II Recalls as a Percentage of Estimated Worldwide Pacing System Sales 1980–1986

Company	No. Sold[a]	No. Recalled[b]	% Recalled
Cordis	208,000	45,603	21.9
Medtronic	629,000	37,000	5.9
Telectronics	150,000[c]	3,777	2.5
Cardiac Pacemakers Inc	125,000	2,466	2.0
Pacesetter	151,000[d]	690	0.5
Intermedics	242,000	293	0.1

[a] Data are from references 9–13. [b] Data are from references 5 and 6. [c] Reference 13 estimates Telectronics sales as follows: 1981, 18,500; 1982, 20,100; 1983, 21,900; 1984, 23,000; 1985, 24,000; 1986, 25,000. From these data, it is projected that 1980 sales were in the range of 17,500 units. [d] Reference 11 indicates that Pacesetter has had about 10% of total pacemaker sales. Taking 10% of worldwide implants for 1986 from reference 12 gives an estimated 26,700 units sold in 1986.

rate and the rates of the others ranged from moderate to low).

Comment

It is evident that the rates of FDA-classified serious recall have differed appreciably among companies manufacturing pacemakers and related products. Although almost 250,000 devices were involved during the 13-year study period, the number of affected patients may be less because an individual could have received both a potentially defective pacemaker and lead. However, this has probably happened infrequently as no manufacturer has had major simultaneous recalls of both pulse generators and leads. On the other hand, a single malfunctioning programmer could potentially adversely affect a number of patients.

Most pacing systems were highly reliable, but a few products and some specific components were associated with a relatively high rate of potentially catastrophic failure. Of even greater concern, there was no overall tendency toward improvement with time (Table 2). Approximately 40% of all recalls during the 13-year study period were recorded within the last 30 months, even though the number of units implanted annually peaked in 1981 [8–13]. Only one company had experienced no class I recalls by the end of the study period, and with the increasingly complex nature of pacemaker and related product technology further FDA actions will inevitably be required. However, because all major pacer manufacturers are involved in development of dual-chamber and antitachycardia devices, the inherent risks should be similar. Furthermore, relatively few problems have been related to these newer, more complex devices despite their increased battery energy requirements.

The percentage of pacing products at risk may be underestimated for some companies by the comparative statistics. In several actions, as indicated in the footnotes to Table 1, the precise number of units involved has not been identified by the FDA, even when the number has been available from other sources [14–16]. Especially when a recall has been extended from a preliminary, relatively small number of devices to include all of a product distributed within a certain time or serial number range, apparently no attempt has been made to provide the additional number of units at risk even when large [14, 16]. Furthermore, on at least two occasions, a substantial number of units were never classified even though they were very similar to those involved in a previous class I or II recall [16–18].

Presenting class I and II recalls as a percentage of worldwide sales (Table 3) may also underestimate the problem because the number of US-manufactured recalled units distributed internationally is not always detailed in FDA data and non–US-manufactured devices are only classified by the FDA if recalled after distribution in the US. Using worldwide sales is still advantageous as it allows normalized comparisons of all but one of the companies whose pacing products have been extensively used in North America during the last 7 years.

Relating the number of units recalled to US sales (Table 4) might slightly overstate the percentage of devices at risk if most internationally distributed units were consistently documented in FDA recall data. However, as indicated in the footnotes to Table 1, this was seldom true. The advantage of this measure is the comparison it allows of the five major North American pacemaker distributors throughout the 13-year period for which sales estimates are available.

The 13-year recall study period was July 1974 through June 1987. The 13-year sales figures are offset 6 months earlier—January 1974 through December 1986. This covers the most recent pacemaker sales data available and, as recalls are initiated some time after distribution and implantation of a device, the small time offset is appropriate. The study period is essentially identical to that of the regularly reported *Performance of Implantable Cardiac Rhythm Management Devices* referred to previously [7]. However, the actuarial device survivals in that report appear much better than would be expected from the class I and II recall rates and from the overall incidence of FDA actions recorded.

The potential for this type of discrepancy has been noted previously [19]. As one example, pulse generators powered by lithium iodine and lithium cupric sulfide chemistries show similar actuarial survivals in the report

Table 4. Devices Subjected to Class I and II Recalls as a Percentage of Estimated US Pacing System Sales 1974–1986

Company[a]	Sold[b]	No. Recalled[c]	% Recalled
Cordis	199,300	64,746	32.5
Medtronic	594,500	58,555	9.8
Cardiac Pacemakers Inc	104,900	3,204	3.1
Intermedics	206,600	1,754	0.8
Pacesetter	107,200	698	0.7

[a] Biotronik and Telectronics are omitted from this table as independent estimates of US sales were not available for this period. [b] Data are from references 8–12. [c] Data are from references 5 and 6.

by Bilitch and colleagues [7]. In contrast, approximately 40% of all FDA recalls have affected the one manufacturer who uses primarily the lithium cupric sulfide power source against only 16% of study period sales. Similarly in 1985, slightly more than half of the "no-output" cases for all of Europe involved Cordis units. The next worst performance was 10% for a European company with minimal North American sales [20]. This does not imply that manufacturers using lithium iodine power cells have not occasionally also produced products with shortened pulse generator life as compared with original projections [21].

There are several reasons why *Performance of Implantable Cardiac Rhythm Management Devices* may overestimate the reliability of some implantable devices. First, models are dropped if "their performance declined either by general removal, recall or failure rate" to the point that there are few units or "the actuarial survival is low" [7] (ie, devices with very poor performance are deleted from that report). Second, what the authors describe as "general withdrawals"and "elective withdrawals" reduce the database rather than the actuarial survival. For patients lost to follow-up, this should not change perceptions of reliability. For models with units removed from the database because of recalls or "physician concern about performance of a particular pulse generator" or concerns related to lead failure, the actuarial survivals reported may be much better than the freedom from intervention interval experienced by patients who have a similar product implanted. According to the authors, "it would be inappropriate to conclude from these data that any implantable cardiac rhythm management device would have a particular functional reliability" [7]. Third, although the sample appears large (more than 15,000 pulse generators followed), it is small compared with the more than 1,300,000 devices implanted in North American patients during the same period. *Performance of Implantable Cardiac Rhythm Management Devices* gives a reasonable assessment of random failures, but it obscures the very substantial occurrence of problems for patients and for physicians who follow those patients related to the relatively high percentage of recalls documented for some products.

Evaluation of the reliability of pacing leads is complicated by the frequent abandonment and nonremoval of dysfunctional implants. Because failed leads are often not returned for analysis, they may not be counted in a manufacturer's database. This compromises estimates of lead reliability. In addition, mechanical design considerations can have a substantial impact on lead reliability. For example, the relative advantages and disadvantages of bipolar versus unipolar pacing have been the subject of prolonged debate. Recent opinion favors the bipolar configuration because of potentially decreased risk of crosstalk, chestwall stimulation, and myopotential inhibition [22, 23]. Recommendations for essentially universal conversion to the bipolar approach should be tempered by the knowledge that most serious lead recalls classified by the FDA have been associated with mechanical failure of bipolar designs.

Although many recent lead problems have been attributed to failure of segmented polyurethane insulating sheaths, virtually no insulation problems have been reported with designs in which polyurethane was not subjected to high amounts of stress during manufacture [24]. The complexity of the problem is illustrated by the Medtronic 6971, a unipolar lead using essentially identical materials and similar "interference-fit" manufacturing as its bipolar counterpart, the 6972. Although its failure rate is higher than those of leads of other manufacturers and earlier silicone-insulated leads, the 6971 has exhibited a much lower failure rate than the bipolar 6972, 2% to 3% at 2 years [15, 25] versus up to 20% at 3 years [16].

Furthermore, there is no reason to assume that the newer in-line bipolar configurations will be structurally more reliable than side-by-side designs of the past. Bipolar construction requires two independent conductors and insulating sheaths. The increased complexity of the distal in-line electrode arrangement [15], the increased lead body stiffness, and the relatively delicate nature of the short separation between anode and cathode in the lead/generator connection of the implanted system [26] may make the risk even greater. In-line bipolar designs will persist because they allow smaller devices and thus the potential for greater patient comfort but, for the foreseeable future, there is a risk that they may compromise reliability and shorten the functional life of implanted pacing systems.

With its limited budget and manpower, the role of the FDA in handling the increasing numbers of recalls related to implantable cardiac rhythm control devices in the last 10 years has been difficult. This is emphasized by the recent tendency to limit the use of recalls and to rely often on Medical Device Safety Alerts, even in potentially life-threatening situations.

Unfortunately, actions have been inconsistent both with respect to individual manufacturers and particular devices. For example, more than 10,000 Cordis Gamma series pacemakers were subject to class I recall in 1984 because early battery depletion led these devices to operate at their end-of-life rate for 2 months rather than an expected 6 months before failure [6]. Thus, for patient safety, increased monitoring frequency and earlier replacement were required. In contrast, more than 1,200 Cordis Stanicor Lambda models subject to high risk no-output failure (1987) and 1,200 Cordis Gemini models at risk for crosstalk inhibition of ventricular output (1985) were classified as Medical Device Safety Alerts [6]. It is notable that, in contrast to the Gamma series, these potentially lethal problems are not always predictable by increased follow-up, no matter how frequent.

As an example of variability in the FDA's handling of a single model series, more than 40,000 Medtronic Xytrons were recalled in six separate actions in a 6-year period, all for premature failure related to moisture intrusion, with a high risk of "no-output modes" [6, 18]. The first five recalls were identified as class II; the last recall involving 20,000 units was identified as an Advisory. No action was taken on numerous other Xytrons although independent follow-up indicated that all were of similarly high risk [18, 19, 27] (ie, up to 12% to 15% incidence of sudden death [19]) and that the number of units at risk and the magnitude of the risk was consistently underestimated [18]. The design of this device was questioned even before its first recall [28], but it was subject to only minor modifications throughout its distribution [19]. Apparently no substantial effort was ever made to limit its availability.

In contrast, all Hancock pericardial patches were recently removed from the market by the Canadian Bureau of Radiation and Medical Devices because a limited number had been incorrectly labeled for species of origin. This was not associated with any known patient risk. Hopefully in the future, enforcement agencies will spend more time and effort defining and dealing with medically high-risk situations, even though elusive, and react less harshly to bureaucratically annoying, easily definable errors like mislabeling if no patient risk is involved.

The previously detailed pacer system problems, in combination with ten recent actions each involving more than 10,000 devices [6], make it apparent that greater efforts are required by the FDA and manufacturers to initiate recalls earlier. The ostrich approach to potential problems has unnecessarily extended the range and duration of several recalls [15, 16, 18, 19, 25]. One highly respected authority has stated "it is obviously advantageous for the manufacturer to delay admission of quality defects for as long as possible" [29]. This serious indictment of the monitoring and enforcement agencies has been independently confirmed. As a result of its review of the FDA's handling of the 6972 lead problems, the US Department of Health and Human Services through its Office of Inspector General recently recommended that a task force be set up to review and improve FDA objectivity and timeliness. Earlier responsible action should help limit the risk to patients, health care providers, and manufacturers.

To facilitate collection of accurate comparative data, the various North American agencies regulating introduction and implantation of pacemakers should demand a best approximation of the number of units involved in each action rather than provide partial or even no numerical data, as in at least three recent classifications. Every potentially life-threatening situation should be objectively classified as I, II, or III based on the available data. The current trend of allowing the spectrum of trivial through life-threatening situations to be handled as Medical Device Safety Alerts should be ended.

Given the frequency of both lead and implantable pulse generator failures and recalls, selection and implantation of a pacemaker that provides noninvasive determination of the implanted power source's voltage and impedance, lead impedance, and functional performance data will improve both patient and follow-up system security. Not all devices in any recalled series will necessarily fail early [30]. For example, even though the 6972, 4002, and 6991U leads are acknowledged to have increased failure rates, 80% or more of these devices are functioning normally 3 years after implantation. Although only a few patients harboring a recalled product usually require reoperation, all such patients need reassurance and frequent accurate follow-up.

Sequential change in stimulation impedance is now widely accepted as a method of trouble-shooting suspected lead failure [30, 31]. Pacemakers with proven real-time telemetry systems allow noninvasive identification (including transtelephonic with two manufacturers' devices) of patients at risk and appropriate reassurance of those not at risk [31]. Furthermore, the frequency with which recalls have been caused by inadequate or lost indirect (rate related) end-of-life indicators is remarkable [32]. Many of these problems could have been safely managed with appropriate telemetry, which may allow the clinician to anticipate and diagnose problems before they become clinically apparent. The availability of real-time telemetry within an implanted device will, in some instances, decrease patient risk due to a potential lead or pulse generator problem to a level at which a lower class FDA recall may be justified.

Conclusion

Over the past 13 years, there have been appreciable differences among pacemaker manufacturers in the incidence of product failures and problems leading to recall. Pacing system failures and large recalls have not been eliminated despite replacement of much less reliable mercury zinc batteries with lithium power cells and replacement of epoxy enclosures with hermetically sealed metal cases. Diligent follow-up of all patients with implanted pacing systems is still required.

Given the frequency of both lead and implantable pulse generator failures and recalls, selection of a system that permits early identification, analysis, and monitoring of problems seems prudent. Specifically, devices that provide noninvasive determination of the implant's battery voltage and impedance, lead impedance, and functional performance data (so-called measured or real-time telemetry) should be used preferentially, assuming they provide the therapeutic capabilities required by the particular patient.

The efficiency and safety of recall management and follow-up have been impeded by inconsistent regulatory actions. Recalls continue to be a risk for all manufacturers and patients, but when problems occur, responsible action should be initiated much sooner than was often the case in the past. The use of nonclassified actions like Medical Device Safety Alerts should be limited, and all life-threatening situations should be classified with consistency. The number of devices involved should be accurately determined.

This report should encourage open discussion and analysis of the sensitive recall issue as well as improvements in the reliability of cardiac pacing system products. Because of the difficulty in assembling and interpreting this information, the inconsistency of regulatory actions, and the deficiencies in current reporting and dissemination, it is understandable that government agencies, physicians, and hospital administrators may perceive no difference in reliability between various products.

The dramatic improvements in pacemaker adaptability and effectiveness achieved over the last 13 years, in association with improved cost-effectiveness, are not negated by the details of this report. However, ample room remains for further improvement.

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Appendix

FDA Device Action Definitions

Recall

Voluntary removal by a firm of a defective product from the market. Some recalls begin when the firm finds a problem; others are conducted at the FDA's request. Recalls may involve physical removal of products from the market or field correction of the problem where the product is located.

Class I: A situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

Class II: A situation in which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences, or in which the probability of serious adverse health consequences is remote.

Class III: A situation in which the use of, or exposure to, a violative product is not likely to cause adverse health consequences.

Medical Device Safety Alert/Medical Device Notification

Any communication issued by a manufacturer, distributor, or other responsible party, or the FDA to inform health professionals or other appropriate persons or firms of a risk of substantial harm from a medical device in commercial use. Safety alerts are issued voluntarily; notifications are issued at the request of the FDA.

Asanguineous Reperfusion in a Canine Model of Cardiopulmonary Bypass and Controlled Postischemic Work

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This study was designed to test the hypothesis that asanguineous reperfusion with a standard crystalloid cardioplegic solution results in improved myocardial salvage after a period of global ischemia. Four groups of 6 dogs each were placed on cardiopulmonary bypass. Control group A (work only) performed two hours of controlled work by contracting against a saline-filled left intraventricular balloon. Control group B (ischemia only) underwent 45 minutes of global normothermic ischemia before simple blood reperfusion while supported on bypass. Groups C and D were subjected to ischemia and reperfusion as in group B, followed by controlled work stress as in group A. Group D, however, received 500 mL of St. Thomas' Hospital solution immediately before blood reperfusion. Morphological analysis showed no significant injury in groups A and B, whereas group C had 11.4% ± 2.4% necrosis of heart mass versus 2.5% ± 1.1% in group D ($p < 0.001$). Biochemical data from left ventricular biopsies showed no significant differences between groups B, C, and D. Functional analyses showed deterioration of diastolic compliance in group C ($p < 0.05$), although a significant difference in systolic functional indexes could not be detected. Myocardial protection and salvage was improved by initial reperfusion with an asanguineous cardioplegic solution versus reperfusion with blood alone.

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Previous research into myocardial protective strategies has focused primarily on the ischemic phase. A 1985 review by McGoon [1] catalogued the key articles on myocardial protection into 43 separate categories, only one of which concerned modification of reperfusion conditions. The traditional concept that the degree of tissue injury resulting from an ischemic insult is determined primarily by the length of the ischemic period has been challenged by many investigators. Buckberg [2] concluded that "[t]he fate of myocardium jeopardized by global or regional ischemia is determined more by the careful control of conditions of reperfusion and composition of the reperfusate than by the duration of ischemia itself." The vast majority of experimental and clinical studies relating to the spectrum of myocardial ischemia injury have used unmodified blood as the reperfusate medium. However, both theoretical rationales and experimental studies suggest that simple blood reperfusion may exacerbate tissue damage after an ischemic insult.

One rational approach to protection during reperfusion is administration of an arresting solution immediately before blood reperfusion. By prolonging arrest during the initial reperfusion phase, metabolic processes could be better channeled toward cellular repair rather than expending needless energy on electromechanical activity. This method was investigated by Follette and colleagues [3] using a blood-based arresting solution with modification of the ionic composition. Menasche's group [4, 5], however, examined use of an asanguineous reperfusion solution in both experimental and clinical studies. They favored a crystalloid solution over modified blood as the reperfusate, citing the greater ease and consistency in preparing a crystalloid solution to a given pH, osmolarity, and ion and substrate composition as opposed to making such adjustments intraoperatively to blood taken from the cardiopulmonary bypass (CPB) circuit. One of the goals of the present study was to determine whether improved myocardial salvage could be obtained using a standard cardioplegic solution (St. Thomas' Hospital [STH] solution) for initial reperfusion.

A second purpose of the study was to attempt a more rigorous test of the effects of asanguineous reperfusion on myocardial protection by subjecting dogs to conditions of CPB, normothermic ischemia, blood reperfusion, and controlled work stress. The work of Menasche's group [4, 5] with an isolated rat heart preparation used oxygenated crystalloid perfusion instead of blood and did not allow comparable control of hemodynamic and work variables. Assessment of myocardial protection in this study was made on the basis of biochemical and functional data as well as a distinct, irreversible, morphological "end point": myocardial necrosis as defined by tetrazolium staining.

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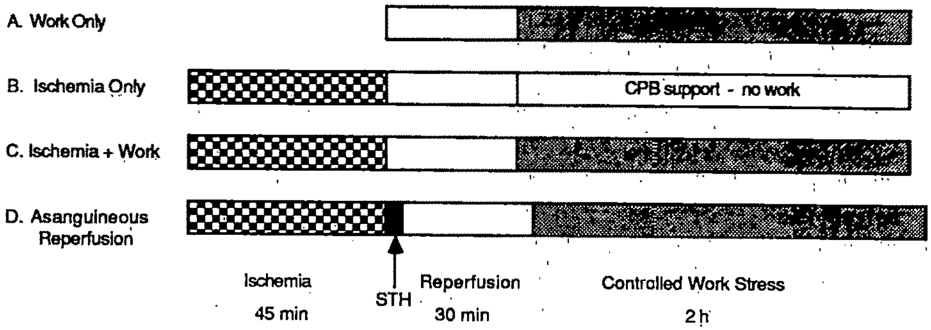

Fig 1. Experimental protocol for groups A through D (CPB = *cardiopulmonary bypass;* STH = *St. Thomas' Hospital solution infused before reperfusion in group D only.)*

Material and Methods

Experimental Groups

The protocol for the experimental groups is shown in Figure 1. Four groups of 6 dogs each were placed on CPB according to the surgical protocol. Control group A received no ischemic insult but were made to perform two hours of isovolumic work by contracting against a saline-filled left intraventricular balloon while supported on CPB. Control group B hearts were rendered globally ischemic by aorta cross-clamping for 45 minutes at 37°C followed by simple blood reperfusion for 30 minutes and then support on CPB for two hours. Dogs in group C were subjected to the same conditions for normothermic ischemia and reperfusion as in group B but were then work-stressed for two hours as in group A. Group D dogs underwent the same protocol as group C dogs except that 500 mL of cold (4°C) STH cardioplegic solution was infused into the aortic root just before the cross-clamp was released. The composition of the STH solution (in millimoles per liter) was as follows: sodium chloride, 110.0; potassium chloride, 16.0; magnesium chloride, 16.0; calcium chloride, 1.2; sodium bicarbonate, 10.0.

Control groups A and B were included in the experimental design to assess whether isovolumic work stress (group A) or 45 minutes of normothermic ischemia alone (group B) resulted in significant necrosis to the extent produced by the combination of ischemia and work stress in group C. Finally, in group D, the effect of asanguineous reperfusion on the degree of myocardial injury produced with ischemia followed by controlled work stress was assessed.

Surgical Protocol

Twenty-four mongrel dogs weighing 25 to 35 kg were obtained from the animal care facilities of the University of Toronto and received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guidelines for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). After induction of anesthesia with sodium thiopental (30 mg/kg), the dogs were intubated and ventilated using a gas mixture of oxygen and nitrous oxide (1:2) with 0.5% to 1.5% enflurane. A right femoral artery catheter was placed to allow continuous monitoring of systemic pressure and repeated arterial blood sampling for hematocrit, blood gases, pH, and activated clotting times. Systemic and myocardial temperatures were measured with thermocouple probes inserted into the esophagus and interventricular septum, respectively.

The heart was exposed through a midline sternotomy and cannulated for CPB after systemic heparinization (5 mg/kg). Venous return was provided by cannulas placed into the superior vena cava through the right jugular vein and into the inferior vena cava through the right atrial appendage. The left femoral artery was used for arterial perfusion with an 18F cannula. A 14-gauge cannula was inserted into the ascending aorta for venting of the left ventricle during the ischemic interval as well as for administration of reperfusion solution in group D dogs.

The bypass circuit was primed with Ringer's lactate solution and replenished with freshly drawn, heparinized, homologous whole blood to maintain the hematocrit greater than 30%. Arterial pH was maintained between 7.35 and 7.45, arterial carbon dioxide tension was maintained between 35 and 45 mm Hg, and arterial oxygen tension was maintained at more than 100 mm Hg by adjusting gas flow and adding sodium bicarbonate as required. After CPB had been established, a compliant balloon was placed within the left ventricle through an apical stab wound for assessment of cardiac function and also for the controlled work stress period in groups A, C, and D. After 30 minutes of CPB, dogs in group A began two hours of controlled work as described below. In group B, C, and D dogs, the ascending aorta was clamped for a 45-minute normothermic ischemic period. A plastic sheet was placed over the sternotomy, and perfusate temperature was adjusted to maintain interventricular septal temperature at 37° ± 1°C. All hearts arrested soon after onset of ischemia and remained arrested throughout the ischemic period. In group D only, 500 mL of cold (4°C) STH cardioplegic solution was infused into the aortic root at the end of ischemia (Fig 1). The aortic cross-clamp was then released in groups B, C and D and, in all cases, spontaneous cardiac activity resumed within three minutes of reperfusion, with defibrillation performed if required. The hearts were maintained in the empty, beating state for 30 minutes of reperfusion. Group B hearts were supported on CPB in the empty, beating state for an additional two hours while groups C and D performed two hours of isovolumic work on CPB by inflating the intraventricular balloon with saline to maintain the end-diastolic pressure at 20 mm Hg.

Assessment of Left Ventricular Function

Left ventricular function was assessed using the intraventricular balloon to obtain systolic and diastolic pressures through a range of balloon volumes from 10 to 50 mL in 5-mL increments. Measurements were obtained at baseline after institution of CPB and were repeated after 30, 90, and 150 minutes of reperfusion (ie, 0, 60, and 120 minutes of work stress). The pressure/volume data were then used to calculate developed (peak systolic minus end-diastolic) pressure and end-systolic elastance (end-systolic elastance = slope of peak systolic pressure versus volume relationship). Developed pressure is expressed as percentage of control values at a balloon volume of 30 mL. This volume produced a left ventricular filling pressure within the physiological range (6 to 12 mm Hg) at baseline. Left ventricular stiffness (compliance^{-1}) was calculated as the slope of the end-diastolic pressure versus volume relationship.

Biochemical Measurements

Myocardial biopsy specimens were obtained by scalpel excision from the outer third of the left ventricular apical wall at baseline, at the end of ischemia, after 30 minutes of reperfusion, and after two hours of controlled work stress. Transmural biopsies were avoided to prevent rupture of the intraventricular balloon. The muscle specimens were immediately frozen in liquid nitrogen and dissected to remove blood and fibrous tissue after freeze-drying. Tissue levels of adenosine triphosphate, creatine phosphate, glycogen, and lactate were analyzed on a Perkin-Elmer or ABA-100 (Abbott) spectrophotometer.

Morphological Examination

After the animals were killed, the hearts were excised, sliced transversely from apex to base in 5-mm sections, and incubated in triphenyl tetrazolium chloride (TTC) solution to delineate areas of necrosis. For verification of the delineation of viable and necrotic tissue by TTC, small biopsy specimens (1 mm^3) were taken from each side of the stained/unstained border for electron microscopic examination. The stained slices were pressed between Plexiglas plates, and areas of viable (stained) and necrotic (unstained) tissue were traced onto acetate sheets for planimetry. The fraction of necrotic muscle per slice was multiplied by the slice weight, and the total sum per heart was recorded as percentage of heart mass.

Table 1. Myocardial Tissue Levels of Glycogen, Lactate, Adenosine Triphosphate, and Creatine Phosphate[a]

	Group			
Substance	A	B	C	D
Glycogen (mg/kg dry wt)				
Preischemia	60 ± 40	52 ± 10	34 ± 12	44 ± 10
End of ischemia	. . .	40 ± 28	18 ± 7	41 ± 28
Reperfusion	79 ± 40[b]	52 ± 18	27 ± 11	43 ± 26
Post-work	69 ± 30	. . .	40 ± 19	52 ± 25
Lactate (mmol/kg dry wt)				
Preischemia	31 ± 16	24 ± 6	20 ± 9	24 ± 7
End of ischemia	. . .	160 ± 3	168 ± 27	152 ± 2
Reperfusion	23 ± 8[b]	41 ± 12	53 ± 22	48 ± 24
Post-work	22 ± 6[b]	. . .	54 ± 24	35 ± 11
Adenosine triphosphate (mmol/kg dry wt)				
Preischemia	17 ± 10	15 ± 8	20 ± 7	24 ± 5
End of ischemia	. . .	5 ± 2	4 ± 3	8 ± 7
Reperfusion	23 ± 6[c]	13 ± 4	12 ± 5	13 ± 3
Post-work	22 ± 3[c]	. . .	12 ± 5	13 ± 5
Creatine phosphate (mmol/kg dry wt)				
Preischemia	12 ± 6	12 ± 5	11 ± 6	11 ± 5
End of ischemia	. . .	7 ± 5	3 ± 3	3 ± 2
Reperfusion	21 ± 12[d]	43 ± 16	47 ± 13	26 ± 17
Post-work	21 ± 7	. . .	37 ± 21	36 ± 23

[a] All values are shown as mean ± standard deviation, n = 6. [b] $p < 0.05$ between group A and group C. [c] $p < 0.05$ between group A and other groups. [d] $p < 0.05$ between group A and groups B and C.

The electron microscopic specimens were immediately placed in fixative solution of 1% glutaraldehyde and 1% paraformaldehyde in phosphate buffer for 24 hours and postfixed in 2% osmium tetraoxide for one hour. The samples were then dehydrated in graded ethanol and acetone, treated with propylene oxide, and cut into 500-Å sections after being embedded. The specimens were mounted on copper grids, stained with uranyl acetate and lead citrate, and examined with a Philips 201 electron microscope. Myocyte ultrastructure was assessed on the basis of criteria for grading of ischemic injury previously reported [6].

Statistical Analysis

All values are expressed as mean ± standard deviation. The groups were compared using one-way analysis of variance; if overall significance was detected, the Student-Newman-Keuls multiple-comparison test was used to specify the significantly different groups. A p value of less than 0.05 was considered significant.

Results

Biochemical Measurements

The measurements of myocardial glycogen, lactate, adenosine triphosphate, and creatine phosphate content are shown in Table 1. Postischemic myocardial glycogen was higher in group A versus group C at the end of reperfusion. Myocardial lactate rose markedly at the end of ischemia, but no differences were noted between the groups subjected to an ischemic interval. Lactate levels

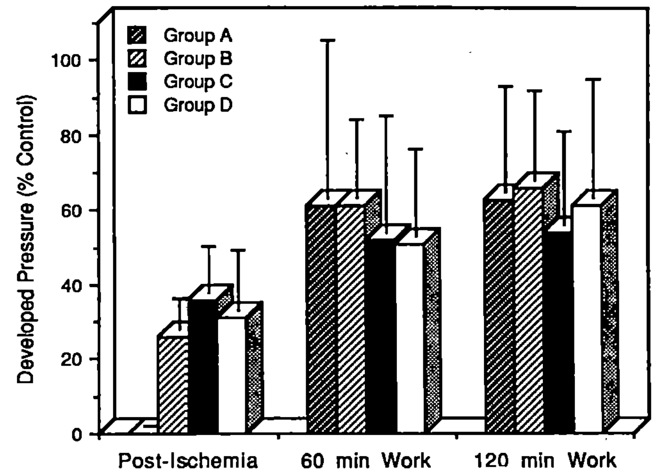

Fig 2. Left ventricular developed pressure expressed as percentage of control at volume of 30 mL (n = 6 per group, mean ± standard deviation).

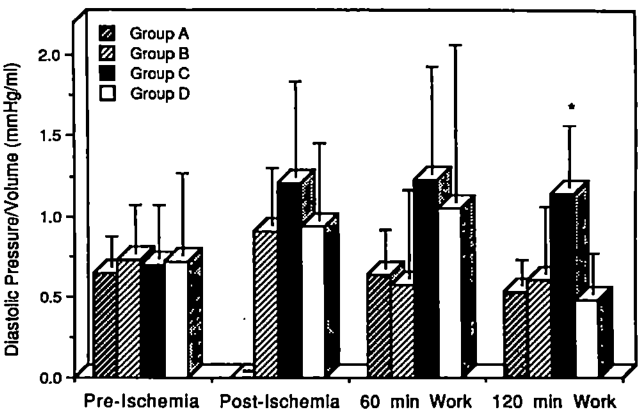

*Fig 4. Left ventricular wall stiffness (slope of end-diastolic pressure–volume relationship) (n = 6 per group, mean ± standard deviation). Analysis of variance between groups at 120 minutes of work; *p < 0.05 between groups C and D.*

remained significantly lower in group A compared with group C throughout reperfusion. Adenosine triphosphate levels in group A (work only) were significantly higher compared with those of other groups, consistent with the absence of an ischemic period in group A. The biochemical data showed no significant differences between groups C and D at any time point.

Left Ventricular Function Assessment

Left ventricular systolic function measurements as represented by developed pressure and end-systolic elastance are shown in Figures 2 and 3, respectively. No significant differences in developed pressure were noted between groups when expressed as percentage of control. End-systolic elastance tended to remain higher in group C versus group D after ischemia and work stress, but the difference did not reach significance ($p = 0.166$). The major functional difference was observed with left ventricular wall stiffness (Fig 4), in which group C showed a marked loss of ventricular compliance after two hours of controlled work ($p < 0.05$).

Morphological Examination

Triphenyl tetrazolium staining revealed significantly ($p < 0.001$) greater myocardial necrosis in group C (11.4% ± 2.5%) versus group D (2.5% ± 1.1%), whereas groups A (0.5% ± 0.7%) and B (0.5% ± 0.5%) had only minimal necrosis (Fig 5). Necrosis in groups C and D was mainly limited to the subendocardial region, whereas small areas of necrosis in groups A and B were randomly distributed within the transmural wall. The reliability of TTC to delineate areas of necrosis was verified with electron microscopy, which revealed normal or minimally injured myocytes in all biopsy specimens of TTC-positive tissue. Lethally injured myocytes were found in biopsy specimens of TTC–negative tissue, with mitochondrial swelling and rupture, fragmentation of cristae, and myofilament contraction-banding.

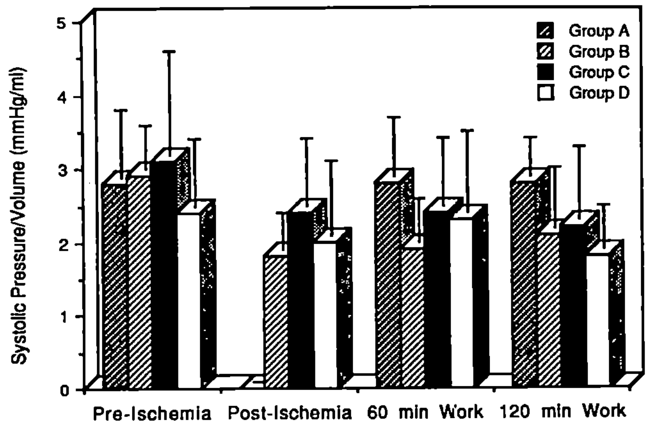

Fig 3. End-systolic elastance values (slope of end-systolic pressure–volume relationship) (n = 6 per group, mean ± standard deviation). Analysis of variance between groups at 120 minutes of work; p = 0.166.

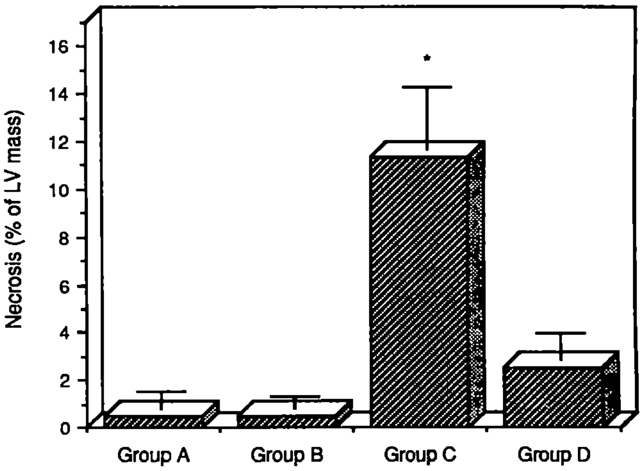

*Fig 5. Left ventricular (LV) necrosis (percentage of left ventricular mass) (n = 6 per group, mean ± standard deviation). Analysis of variance between groups; *p < 0.001 between group C and other groups.*

Comment

The minimal injury observed in groups A and B indicates that neither the controlled work protocol alone nor the ischemia/reperfusion protocol alone was responsible for the extent of necrosis observed in group C, in which ischemia/reperfusion was combined with isovolumic ventricular work loading. These findings are consistent with the hypothesis that left ventricular unloading will favorably influence myocardial recovery after an ischemic interval. Lachsinger and colleagues [7] demonstrated significant reduction of infarct size with adjunctive left ventricular loading in a canine model of regional normothermic ischemia and reperfusion. Similar results were reported by Mickleborough and co-workers [8] and Axelrod and associates [9] and were the basis on which we developed this model of ischemia and ventricular loading to test the use of an asanguineous reperfusion solution.

Administration of STH solution after an ischemic interval and immediately before blood reperfusion was effective in limiting infarct size by a factor greater than fourfold in group D compared with group C. Therefore, the difference between groups C and D reflects the effectiveness of asanguineous reperfusion over simple blood reperfusion in postischemic myocardial salvage.

In contrast to the morphological findings, the biochemical results revealed no significant differences between groups C and D at any time point. A possible explanation for this apparent inconsistency would be the existence of a transmural gradient of biochemical changes that would not be detected by biopsy specimens harvested from only the outer third of the myocardial wall. As expected, necrosis in groups C and D was limited to the subendocardial region; it has been well established that ischemic necrosis develops transmurally from subendocardial to subepicardial layers in the working dog heart [10]. Biopsy specimens, however, were limited to the outer third in this experiment to avoid rupturing the intraventricular balloon required for functional assessment and controlled work. We do not believe that the differences between morphological and biochemical data suggest an error in the validity of the TTC enzyme-mapping technique. Although Barnard and colleagues [11] have reported failure of TTC staining to delineate areas of necrosis under certain conditions, we verified the necrotic border zone by electron microscopy; it consistently and accurately distinguished between necrotic and viable tissue.

Analysis of left ventricular developed pressure failed to reveal any difference between groups at a level considered statistically significant. Use of developed pressure may not be a sufficiently sensitive technique to detect the systolic functional deficit created by only 11.4% necrosis after a period of reperfusion and work stress of two hours.

End-systolic elastance measurements tended to be higher in group C versus group D, although the sample size of 6 dogs per group may have limited the power of the experimental data to reach statistical significance. This may appear to suggest that contractile function was superior in the group not receiving asanguineous reperfusion. Although the ideal measure of systolic function remains controversial, Suga and Sagawa [12, 13] originally demonstrated end-systolic elastance to reflect the state of myocardial contractility and found it to be unaffected by preload and afterload over a physiological range of ventricular volumes. However, end-systolic elastance may not be a reliable indicator of function when the heart contains nonuniform, "patchy" necrosis [14]. Necrosis probably results in contracture at each locus of infarction and ventricular filling to the same internal volume as previously would cause stretching and increased tension of the surrounding viable myocardium. The increased length and tension of the sarcomeric units would then result in locally increased contractility and an overall increase in end-systolic elastance values despite a decrease in useful cardiac hemodynamic function. This interpretation appears to be valid for our data, which showed a significant loss of ventricular compliance as the slope of the diastolic pressure/volume relationship was markedly elevated in group C compared with group D ($p < 0.05$).

The concept that postischemic recovery is improved when the heart is kept arrested during early reoxygenation was initially reported in 1960 by Danforth and co-workers [15], who demonstrated more consistent repletion of adenosine triphosphate levels during reperfusion in the arrested versus the nonarrested heart. Follette and colleagues [16] proposed that maintaining arrest during the initial minutes of reperfusion might allow oxygen and metabolites to be diverted toward cellular repair rather than electromechanical activity. Lazar and associates [17] introduced the term "secondary warm blood cardioplegia" and reported "reversal" of global ischemic injury through further application of this concept. Continuing work by the same group has included various compositional modifications in blood cardioplegic reperfusates [18].

The concept of reducing postischemic or reperfusion injury with use of "surgical" versus "medical" (unmodified blood) reperfusion is supported by the work of other investigators. Wood and associates [19] showed that initial reperfusion of an ischemic zone with crystalloid or blood cardioplegia limits infarct size compared with simple blood reperfusion. Comparable results were reported by Franco and colleagues [20], although they obtained better results with cold crystalloid reperfusion of the locally ischemic segment compared with blood cardioplegic reperfusion. Menasche and colleagues [4, 5] focused on the use of asanguineous reperfusion solutions in experimental and clinical studies. They concluded that an asanguineous reperfusion solution provides improved functional recovery when its composition is modified with respect to electrolytes, pH, and substrates. More recent results comparing surgical and medical reperfusion were reported by Davis and colleagues [21] and Miller and co-workers [22]; both groups showed a reduction in necrosis or improved functional recovery with crystalloid reperfusion versus simple blood.

The results of this study allow only speculation as to possible mechanisms by which a cardioplegic crystalloid solution as the reperfusate might influence reperfusion damage. The proposal that oxygen and metabolites could be better used for cellular reparative processes would not theoretically apply with this protocol in which the crystalloid solution was not oxygenated. However, the potential role of cytotoxic oxygen metabolites or free radicals in causing cellular damage may offer a possible advantage of crystalloid over simple blood or blood cardioplegic reperfusion. Whereas free radical scavengers could be added to either a blood or crystalloid reperfusate, with blood cardioplegia there exists the possibility of free radical-mediated injury due to the higher oxygen tension of an oxygenated solution as well as the controversial role of neutrophil involvement in blood-based solutions. Creswell and colleagues [23] showed in isolated rabbit hearts that recovery of myocardial function after an ischemic interval is optimal when unoxygenated rather than oxygenated reperfusates are used. These investigators also reported data indicating that free radical scavengers (superoxide dismutase and catalase) were effective in ameliorating the injury observed with an oxygenated reperfusate. Furthermore, reperfusion with an asanguineous solution before reoxygenation might also be effective in removing free radical precursors that accumulated secondary to adenine nucleotide degradation.

One possible mechanism by which STH solution might be effective in reducing necrosis is the known interaction of the elevated magnesium concentration in this solution (16 mmol/L) with cellular calcium flux. Janke and colleagues [24] demonstrated that elevated plasma magnesium levels are effective in reducing isoproterenol-induced calcium uptake and necrosis. At a more basic level, magnesium has been shown to modify the function of the sarcoplasmic reticulum in promoting removal of calcium from the myofibrillar space and can also suppress calcium's ability to stimulate myofibrillar adenosine triphosphate activity [25, 26].

Improved myocardial salvage with cold asanguineous reperfusion may also involve the effect of temperature change on intracellular calcium movement. Okada [27] recently reported improved recovery from anoxia in rat hearts exposed to a short period of "cold shock" and proposed that relief of mitochondrial calcium overload by rapid temperature reduction might facilitate metabolic and functional recovery.

The role of hyperosmolar solutions in preventing edema during reperfusion has been considered by numerous investigators, but opinion varies as to its effectiveness [28, 29]. Whether STH solution (324 mosm/L) is sufficiently more hyperosmolar than blood to play a substantial role could be disputed. The minimal buffering capacity of STH solution (sodium bicarbonate = 10 mmol/L at pH 7.8) also appears not to be a major factor influencing reperfusion.

The experimental protocol used in this study includes a substantial ischemic injury (45 minutes at normothermia), which would simulate the clinical condition of acute preoperative myocardial ischemia. Although normothermic ischemia without previous cardioplegic protection does not mirror elective cardiac operation, this protocol was chosen to induce an injury severe enough to allow detection of differences by morphological and functional criteria. Furthermore, the results of this study do not allow conclusions to be made regarding the efficacy of "standard" versus "specially formulated" reperfusion solutions as only STH solution and unmodified blood were directly compared.

In conclusion, despite widespread interest in modifying the conditions of reperfusion to reduce postischemic injury, most clinical centers simply remove the cross-clamp and reperfuse with unmodified blood. The experimental protocol used in this study has emphasized the principle of technical simplicity in demonstrating that myocardial protection and salvage can be improved when a standard crystalloid cardioplegic solution (STH) is infused just before reperfusion, as opposed to use of unmodified blood reperfusion. The goal now is to identify fundamental cellular mechanisms through which reperfusion injury can be controlled.

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Valve Replacement in the Right Side of the Heart in Children: Long-Term Follow-up

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Twenty-five patients (16 male, 9 female) underwent right-sided valve replacement (10 pulmonary valve replacement, 14 tricuspid valve replacement, 3 tricuspid plus pulmonary valve replacement, and 2 replacements of a single atrioventricular valve) at the University of Nebraska Medical Center from June 1977 to December 1986. Twenty-one patients (84%) are long-term survivors with 2,035 months follow-up (range, 41 to 143 months; mean, 96.9 months). Twenty-three Carpentier-Edwards bioprosthetic valves, one Ionescu-Shiley bioprosthetic valve, and nine St. Jude Medical valves were inserted. Follow-up of 17 patients with a Carpentier-Edwards valve ranged from 5 years 9 months to 11 years 9 months (mean, 8 years 11 months). To date there has been one reoperation after 3 years 4 months in this group. One patient who received an Ionescu-Shiley bioprosthesis required re-replacement at 20 months after operation. Three of 4 patients who received St. Jude mechanical valves and are long-term survivors have required replacement after 36 to 56 months. We conclude that the Carpentier-Edwards bioprosthetic valve is a viable option in the right side of the heart in the young age group when annular size is adequate to accommodate an appropriate bioprosthesis.

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Although valve reconstruction is preferable, some children require prosthetic valve replacement. Choosing the appropriate valve for a child requires consideration of the valve flow characteristics, the need for anticoagulants and their consequent risks, thrombosis risk, and long-term durability. Small numbers of children who have survived right-sided valve replacement and have had long-term follow-up are reported. Data are commonly extrapolated from the reports of valve replacements in adults [1] or from reports of valves in the left side of the heart in children [2]; this may not be valid. This report describes the results to date in 25 young patients who underwent right-sided valve replacement during a 9-year 6-month period at the University of Nebraska Medical Center.

Material and Methods

The hospital charts of all 25 patients (16 male, 9 female) who underwent a right-sided valve replacement at the University of Nebraska Medical Center between June 1977 and December 31, 1986, were reviewed. Patients who underwent a Fontan procedure or placement of valved conduits were excluded. Patient age at the time of initial prosthetic right-sided valve placement ranged from two days to 20 years (median, 8 years 2 months). Diagnoses included tetralogy of Fallot, 6 patients; absent pulmonary valve syndrome, 3 patients; Ebstein's anomaly, 3 patients; endocarditis, 2 patients; previous pulmonary valvectomy, 4 patients; univentricular heart complex, 2 patients; endocardial cushion defect, 2 patients; polyvalvular disease, 1 patient; and congenital tricuspid valve regurgitation, 2 patients (Table 1). Current follow-up was available for all except 4 patients who had moved from the area in the past 1 to 2 years.

Results

Carpentier-Edwards Tissue Valve

Carpentier-Edwards porcine valves (23 valves in 18 patients) were used early in the series; 17 of 18 patients are current survivors. Patient age at the time of initial placement ranged from three days to 20 years (median, 10 years 4 months). Follow-up since implantation ranged from 5 years 9 months to 11 years 9 months (mean, 8 years 4 months). The nonsurvivor was a three-day-old infant with absent pulmonary valve syndrome who died intraoperatively.

One patient with a Carpentier-Edwards porcine valve has required replacement. At the time of reoperation, 40 months after his initial valve replacement, one leaflet of his bioprosthetic valve was adherent to the ventricular wall, allowing valve regurgitation. Pathological examination showed several focal calcific deposits on one cusp of the explanted valve. This patient had previously undergone both aortic and tricuspid valve replacement due to polyvalvular disease. The tricuspid valve was replaced, although this was not clinically necessary at the time of required aortic valve replacement to minimize risk of a separate open heart procedure for tricuspid valve replacement. The Carpentier-Edwards valve in the tricuspid position was replaced with another Carpentier-Edwards, which at 60 months required balloon dilation for stenosis.

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Table 1. Preoperative Diagnosis for Patients Undergoing Right-Sided Valve Replacement

No. of Patients	Initial Diagnosis	Mean Age at Time of Initial Valve Replacement	Position of Valves	Outcome
6	Tetralogy of Fallot	107 mo	3 TVR + PVR 3 PVR	All alive
3	Tetralogy of Fallot with absent pulmonary valve	45 mo	3 PVR	1 DOT (2 days old)
3	Ebstein anomaly + VSD + ASD	161 mo	3 TVR	All alive
4	Pulmonary stenosis, 2 Noonan's syndrome	183 mo	4 PVR	All alive
2	Endocarditis	180 mo	2 TVR	All alive
2	Univentricular heart complex + congenital AV valve regurgitation	48 mo	2 AV valve replacement	2 St. Jude Medical valves, 1 DOT, 1 died 2 wk postoperatively
2	Congenital TR + multiple VSD	40.5 mo	2 TVR	1 died 8 days postoperatively (St Jude Medical valve)
2	Endocardial cushion + TGV + tetralogy of Fallot	54 mo	2 TVR + 1 RV to PA conduit[a]	Both alive
1	Polyvalve disease (aortic stenosis)	9 yr	TVR + AVR with Konno annuloplasty	Alive and well

[a] Conduit not included in study.

ASD = atrial septal defect; AV = atrioventricular; AVR = aortic valve replacement; DOT = died on table; PA = pulmonary artery; PVR = pulmonary valve replacement; RV = right ventricle; TGV = transposition of great vessels; TR = tricuspid regurgitation; TVR = tricuspid valve replacement; VSD = ventricular septal defect.

The original tricuspid valve replacement was performed at age 9 years 3 months, with re-replacement at 12 years 7 months. Patient weight had increased from 27 to 38 kg in the interim. No other patient has required re-replacement.

At present, 14 patients have had recent echocardiography. The one patient with balloon dilation had good results; of the 2 other patients with echocardiographic findings consistent with combined stenosis and insufficiency, 1 has evidence of calcification. Both await balloon dilation. One patient has had both tricuspid valve replacement and pulmonary valve replacement; the pulmonary valve is functioning with only moderate pulmonary insufficiency but the tricuspid valve has moderate stenosis and insufficiency. Both patients are clinically asymptomatic. Six patients have echocardiographic diagnosis of stenosis (10 to 20 mm Hg estimated gradient) or mild to moderate insufficiency across their prosthetic valves, or both. Five patients have echocardiographic readings in the normal to mildly insufficient range; these findings were not different based on length of follow-up. Follow-up of patients with normal or nearly normal findings ranged from 8 years 3 months to 11 years 9 months; that of patients with moderately severe insufficiency ranged from 5 years 11 months to 11 years 3 months from implantation, and that of patients with echocardiographic diagnosis leading to a need for intervention ranged from 5 years 7 months to 11 years 11 months. Age at valve placement also did not correlate with long-term function (range, preschool to teenage in each group).

Ionescu-Shiley Pericardial Valve

The single Ionescu-Shiley tissue valve placed in the tricuspid position required replacement 20 months after implantation. The explanted valve showed ingrowth and retraction of cuspal tissue without calcification. The patient's age at the time of initial implantation was 4 years 6 months.

St. Jude Medical Valve

Seven patients have received a total of nine St. Jude Medical valves. Patient age at the time of operation ranged from 2 weeks to 8 years 2 months (mean, 4 years 6 months) at initial valve replacement. Three patients died in the hospital; 2 of these patients had univentricular heart complex (age, 2 weeks and 8 years 2 months); the third, a 9-month-old child, had complex congenital heart disease including multiple ventricular septal defects and congenital tricuspid regurgitation. None of the nonsurvivors died of prosthetic valve malfunction (Table 2).

There have been no late deaths in the remaining 4 patients. Three of the 4 patients have required re-replacement between 13 and 22 months after initial replacement. They have been followed for an average of 65 months after initial placement. The St. Jude Medical valves have been in place for 35 to 56 months (median, 54 months). Two patients were initially discharged on warfarin plus aspirin; 1 of these patients required hospitalization for hemothorax and is subsequently being treated with warfarin only. One patient on warfarin plus dipyridamole has had three episodes of valve dysfunction (immobile left leaflet) secondary to thrombus diagnosed by echocardiography; he was treated successfully with streptokinase or urokinase each time. Another patient who underwent streptokinase infusion 23 months after valve placement for an immobile leaflet demonstrated by echocardiography and physical examination did not improve. He subsequently underwent placement of an aortic

Table 2. Nonsurvivors After Right-Sided Valve Replacement

Patient	Age at Operation	Weight (kg)	Diagnosis	Operation	Cause of Death
1	3 days	3.5	Absent pulmonary valve syndrome, ASD, VSD	Repair ASD, VSD, placement of Carpentier-Edwards 23-mm pulmonary valve	DOT
2	15 days	3.4	S/P repair CoAo, S/P PA band, TGV, single ventricle, single AV valve, AV valve regurgitation 4+	Placement of No. 19 St. Jude valve	Ventricular dysfunction, first postoperative day
3	8 yr	19.8	TGV, mitral atresia, univentricular heart, S/P repair CoAo, S/P Blalock-Hanlon, S/P PA band, S/P Blalock-Taussig shunt, S/P pacemaker, TI (single AV valve)	Placement of No. 29 St. Jude valve	DOT, unable to be weaned from bypass
4	1 yr	8.7	S/P repair of multiple VSDs and ASD, Down's syndrome, PAH, TI 4+	Placement of No. 19 St. Jude valve 3 wk after initial repair due to continuing clinical deterioration	Multiorgan failure 9 days postoperative

ASD = atrial septal defect; AV = atrioventricular; CoAo = coarctation of aorta; DOT = died on table; PA = pulmonary artery; PAH = pulmonary artery hypertension; S/P = status post; TI = tricuspid insufficiency; TGV = transposition of great vessels; VSD = ventricular septal defect.

homograft in the pulmonary position at another institution after he moved from the area. Thrombus on the valve was reported at the time of explantation. He was on aspirin plus dipyridamole at the time. The explanted tricuspid valves were described by the pathologist as having fibrous ingrowth of tissue rather than mechanical obstruction from implant technique on two valves. The operating surgeon reported that thrombus was interfering with function in the valve in the pulmonary position (Table 3).

Comment

Of the total reported number of prosthetic cardiac valves placed, those required on the right side of the heart comprise a small percentage [1–14]. A recent article by Pasque and colleagues [7] summarized 26 reports totaling 129 children who had undergone tricuspid valve replacement. Other studies have described right-sided valve replacements in specific disease entities, including two studies with a total of 13 patients with Ebstein's anomaly [11,12]. Follow-up ranged from 1 to 13 years in the 5 patients reported by Bove and Kirsh [11]; no major complications occurred in either the 2 patients with porcine valves or the 3 patients with mechanical valves. This is in contrast to the report by Abe and Komatsu [12], in which 7 of 8 survivors were followed 3 to 18 years. One patient had a porcine valve and 6 patients had a mechanical valve; 3 patients had late death, 1 with thrombosis. Other researchers have investigated pulmonary valve replacement after repair of tetralogy of Fallot [10,13]. The follow-up ranged from 1 to 10 years in the report of Ilbawi and co-workers [10] of 49 patients with porcine valves with an actuarial survival of 84% at 10 years compared with the relatively short follow-up of 12 patients for 5 months to 3 years reported by Misbach and colleagues [13], in which two types of tissue valves and one type of mechanical valve were used with no major complications.

In studies specifically investigating St. Jude Medical valves in children a 2-year actuarial survival rate of 100% was reported for valves in the systemic circulation compared with a 70% 2-year actuarial survival rate for right-sided valves [6]. Similar concern about use of St. Jude Medical valves in the right side was expressed in the report by Miyamura and associates [15]. These investigators reported (1) 1 late death caused by cerebrovascular hemorrhage; (2) need for re-replacement of the single tricuspid valve; (3) need for two treatments with thrombolytic enzyme therapy in one of five pulmonary valves; and (4) no morbidity or mortality in 2 of 5 patients [15]. Children and adults may have different results with a St. Jude Medical valve in the tricuspid position [16,17]. Singh and co-workers [18] reported no morbidity or mortality in 7 adults aged 33 to 71 years (mean follow-up, 13 months). Our results with the St. Jude Medical prosthesis in the right side of the heart are similar to those reported by Ilbawi and co-workers [10] and Miyamura and associates [15], with thrombotic complications in both the tricuspid and pulmonary valve position.

Many studies of larger groups of patients undergoing valve replacement have included right-sided valves in their total. Janusz and associates [1] reported a group of 700 patients aged 8 to 81 years with only 6 (0.86%) undergoing right-sided valve replacement. Similarly, reports of valves replaced in children and young adults aged to 20 years included right-sided valves as part of the total. The number of patients (581) and the percentage of patients receiving right-sided valves (66 of 581 or 11%) is as follows: Gardner and colleagues [3], 9 of 24 (37.5%); Sanders and co-workers [4], 4 of 44 (10%); Spevak and

Table 3. Outcome of Long-Term Survivors With St. Jude Valves

Patient	Initial Diagnosis	Age at First Valve Replacement	Present Anticoagulation	Valve Dysfunction	Medical or Surgical Intervention
1	Tetralogy of Fallot (severe), AI, TI	PVR at 2 yr	ASA + persantine	Immobile leaflet	Streptokinase (no change); re-replacement with aortic homograft
2	Tetralogy of Fallot with absent pulmonary valve	PVR at 5 yr 3 mo	Coumadin + ASA, changed to ASA + persantine	Immobile leaflet	Re-replacement with St. Jude Medical valve; echocardiography showed 14-mm gradient at 56 mo
3	Ebstein's anomaly + VSD	TVR at 4 yr 3 mo	Coumadin + ASA, changed to ASA + persantine	Immobile leaflet	Re-replacement with St. Jude Medical valve; streptokinase 4 mo after second valve with return to function; urokinase 9 mo after second valve; good function shown by echocardiography at 37 mo
4	Endocardial cushion defect	4 yr 6 mo	Coumadin	Functional at 48 mo	St. Jude replaced with Ionescu-Shiley; hospitalized for hemothorax due to anticoagulant; good function shown by echocardiography at 82 mo

AI = aortic insufficiency; ASA = aspirin; PVR = pulmonary valve replacement; TI = tricuspid insufficiency; TVR = tricuspid valve replacement; VSD = ventricular septal defect.

associates [5], 2 of 63 (3.2%); Makhlouf and colleagues [2], 8 of 273 (2.9%); Ilbawi and co-workers [6], 16 of 36 (44%); Wada and colleagues [8], 4 of 44 (10%); Williams and associates [16], 20 of 49 (41%); and Sade and colleagues [17], 3 of 48 (6%). The total valve experience in children is often used to determine the type of valve to use in the right side, although some reports show that right-sided valve patients suffered greater morbidity and mortality compared with children with valves in the systemic circulation [2–6, 16, 19–23]. Sanders and co-workers [4] reported 3 of 4 patients with complete heart block after tricuspid valve replacement, and Makhlouf and colleagues [2] reported 5 of 8 patients with thrombosed prosthetic tricuspid valves. In the group of 8 patients undergoing tricuspid valve replacement reported by Abe and colleagues [12], there was one intraoperative death and three late deaths. The reported types of valves used in the right side of the heart include Starr-Edwards, Björk-Shiley, St. Jude Medical, Carpentier-Edwards, Hancock, Ionescu-Shiley, and "porcine or tissue" (manufacturer not specified). The risk of calcification of tissue valves is well documented, especially in the young age group [21–25]. With the large number of valve types and the small number of valve replacements, it is difficult to conclude from current reports that one type or brand is better than another.

Our results with the Carpentier-Edwards porcine valve are encouraging. The valves were in place longest (5 years 9 months to 11 years 9 months) with few valve complications, except in 1 patient who underwent valve re-replacement at the time of aortic valve re-replacement. Although data are limited for studying the long-term durability of the Carpentier-Edwards porcine valve, the short-term results (up to 11 years 9 months) without the attendant risks of anticoagulant therapy lead us to prefer the Carpentier-Edwards porcine valve. The exception is in small infants, for whom the St. Jude Medical valve's excellent flow characteristics are believed to provide a distinct hemodynamic advantage.

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Transatrial Membranotomy for Budd-Chiari Syndrome

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In a 7-year period, transatrial membranotomy was performed in 11 patients with membranous obstruction of the inferior vena cava. There were 5 men and 6 women, ranging in age from 23 to 53 years. Clinical symptoms included jaundice in 4 patients, hepatomegaly in 4, leg edema or varicose veins in 10, and venous collaterals over the abdominal and chest wall in all 11 patients. Transatrial membranotomy was performed through a median sternotomy in all patients. When inferior vena cava venography revealed that the obstruction was accompanied by long segmental thrombosis, additional dilation was performed with a Hegar dilator. There was no surgical mortality. Early operative complications included pulmonary embolism in 2 patients and bleeding requiring reoperation in 1. In a mean follow-up period of 30.6 months (range, 2 to 88 months), 9 patients had no symptoms, transient pericardial constriction developed in 1 patient and resolved 1 month later, and restenosis of the inferior vena cava developed in another patient 1 year after the first operation. This latter patient received a second transatrial membranotomy followed by percutaneous balloon angioplasty of the inferior vena cava, with a satisfactory result at 8 months follow-up. We conclude that transatrial membranotomy is an effective and safe procedure for patients with membranous obstruction of the inferior vena cava.

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Budd-Chiari syndrome is caused by obstruction of the hepatic venous outflow. Many causes of this syndrome are recognized, including pregnancy, use of oral contraceptives, leukemia, polycythemia rubra, polycythemia vera, tumors, and miscellaneous disorders. A congenital web or membranous obstruction at the level of the hepatic portion of the inferior vena cava (IVC) can also cause Budd-Chiari syndrome and more often occurs in Orientals, especially Japanese [1, 2]. The results of medical treatment of this syndrome are poor [3]. The first case was reported to Osler [4] in 1878, and Kimura and co-workers [5] achieved the first successful surgical correction of this anomaly by transcardiac membranotomy in 1962. For this report, we reviewed 11 patients with Budd-Chiari syndrome due to membranous obstruction of hepatic portion of the IVC. All patients received transatrial membranotomy.

Material and Methods

From August 1978 to October 1985, 11 patients in Chang Gung Memorial Hospital were proved to have membranous obstruction of the hepatic portion of the IVC. They received a complete history review, physical examination, abdominal sonogram, liver scan, blood chemistry, and angiogram with simultaneous catheterization of the right atrium and IVC venogram. Of these 11 patients, 5 were men and 6 were women. Their ages ranged from 23 to 53 years (mean age, 39 years). The clinical symptoms of these patients were jaundice, bleeding esophageal varices, and hepatomegaly in 4 patients; ascites and leg edema or varicosities in 10 patients; and engorged collateral veins over the abdominal and chest wall in all 11 patients (Table 1).

An angiogram with simultaneous catheterization of the right atrium and IVC was performed in all patients. The patients were classified into three groups by angiography [3]: (1) membranous obstruction only, in which the right atrium and IVC venogram showed a membrane between the right atrium and IVC; (2) membranous obstruction with short segmental thrombosis, in which the venogram showed a short obstruction between the right atrium and the IVC, with the length of the thrombus shorter than two vertebrae; and (3) membranous obstruction with long segmental thrombosis, in which the thrombus was longer than two vertebrae. The first group comprised 4 patients, the second group 3 patients, and the third group 4 patients.

Transcardiac membranotomy, first described by Hirooka and Kimura [2], was used in all patients. For patients in the third group, transcardiac membranotomy was performed digitally first; the obstructed long segment of IVC was then dilated with a 36 to 40F Hegar dilator. A perfusion lung scan was performed routinely on the first and eighth postoperative day. An angiogram of the IVC was performed in every patient before discharge from the hospital. Anticoagulation with Coumadin (crystallin warfarin sodium) was continued for 6 months postoperatively.

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Table 1. Clinical Symptoms of Budd-Chiari Syndrome

Patient No.	Age (yr)[a]	Sex	Jaundice	Ascites	Leg Edema or Varicosities	Esophageal Varices Bleeding	Hepatomegaly	Venous Collateral in Abdomen and Chest Wall
1	27	F	+	+	+	−	+	+
2	28	M	+	+	+	−	−	+
3	41	F	−	+	+	+	−	+
4	50	F	−	+	+	−	−	+
5	53	F	−	+	+	+	−	+
6	46	M	+	+	+	−	−	+
7	41	M	−	+	+	+	−	+
8	35	M	+	−	+	−	+	+
9	23	M	−	+	+	+	−	+
10	36	F	−	+	−	−	+	+
11	44	F	−	+	+	−	+	+
Total			4	10	10	4	4	11

[a] Mean age = 39 years.

Results

All patients had regular follow-up ranging from 2 months to 88 months (mean, 30.6 months). There were no surgical deaths; however, postoperative complications were not uncommon. One patient had postoperative bleeding from a collateral vein requiring reoperation for hemostasis. Three patients required a patch of bovine pericardium to close the pericardium because direct closure of pericardium induced hypotension and elevated central venous pressure. One of these 3 patients, a woman with exertional dyspnea, engorged neck vein, ascites, and lower leg edema in the postoperative period, underwent recatheterization of the heart and IVC venogram on the seventh postoperative day. The IVC was patent, but a square root sign was evident in the left ventricular pressure curve and diastolic pressures in all four cardiac chambers were equal. Pericardial constriction was evident. There was no evidence of emboli in the pulmonary arteriogram and perfusion lung scan. Her symptoms and signs disappeared gradually over the next month.

Routine postoperative perfusion lung scan showed that 2 patients had pulmonary emboli. One patient was asymptomatic; the other patient required prolonged ventilatory support for six days after operation, but was discharged from the hospital uneventfully. These 2 patients had preoperative inferior venograms that showed membranous obstruction and a segment of thrombosis longer than two vertebrae.

The symptoms of 1 patient in group 3 recurred 1 year after operation. Simultaneous catheterization of the right atrium and inferior venogram in this patient showed a short segmental thrombosis of the IVC. Transatrial thrombectomy was performed again. However, because the clinical symptoms did not improve after the second operation, transfemoral venous balloon dilation of the IVC was performed four times in 2 weeks before the symptoms subsided. Eight months later, follow-up venograms revealed patency of the IVC without a pressure gradient between the right atrium and the IVC.

Comment

Budd-Chiari syndrome is caused by membranous obstruction of the hepatic portion of the IVC, and occurs frequently in Japanese patients [1, 2, 5–8]. In other countries, such as India [9], Taiwan [10], the United States [11–14], Spain [15, 16], and Germany [17], sporadic cases have been reported. Kimura and colleagues [5] successfully performed the first correction of this disease with transatrial membranotomy in 1962. After reviewing 150 cases, Hirooka and Kimura [2] proposed that this disease has a congenital origin. They also evaluated the different surgical methods used to treat 74 patients who underwent operation in Japan for membranous obstruction of the hepatic portion of the IVC, concluding that transatrial membranotomy is superior to other methods such as balloon catheter dilation, bypass grafting, or excision of the obstructed portion of the IVC. In our experience, the results of transatrial membranotomy are satisfactory and the long-term results up to 88 months after operation are encouraging (Table 2).

Eguchi and co-workers [6, 7] advised that surgical treatment of this disease should depend on whether the obstruction is solely membranous or is associated with a segment of thrombosis. This series comprised 4 patients with membranous obstruction and a long segment of thrombosis. For this group of patients, the procedure was transatrial finger fracture of the membrane and evacuation of the thrombus digitally through a right atriotomy. This was followed by repeated dilation using a 36 to 40F Hegar dilator while the abdomen was open so that the surgeon could guide the Hegar dilator into the abdominal portion of the IVC and prevent perforation of the vena cava. The follow-up cardiac catheterization and angiogram within 2 weeks in these 4 patients showed mild narrowing of the hepatic portion of the IVC but no significant pressure gradient (4 mm Hg).

The pathogenesis of the narrowing of the hepatic portion of the IVC after membranotomy is not yet clear. Compression by hypertrophy of caudate lobe of the liver has been suggested [3]; however, liver scans performed in 10 of these patients showed no evidence of caudate lobe hypertrophy. Abdominal sonogram in these 10 patients also confirmed the absence of caudate lobe hypertrophy. Symptoms recurred 8 months postoperatively in 1 patient. Despite a second operation with transatrial membranotomy, the follow-up venogram showed severe stricture at the hepatic portion of the IVC; the stricture was relieved by repeated percutaneous transvenous (femoral vein) balloon catheter dilation. From this limited experience, we suggest that reoperation with transatrial dilation for patients with recurrent symptoms may be useless. Instead, repeated tranvenous balloon dilation is advised. This suggests that the pathogenenesis of segmental stricture of the hepatic portion of the IVC results from a fibrotic, thickened IVC wall, as described by Okuda and Ostrow [18].

Transient pericardial constriction may occur immediately after operation due to the sudden increased venous return directly from the IVC. It can be managed by enlarging the pericardial cavity with a patch of bovine pericardium.

Two patients in group 3 had evidence of pulmonary emboli after operation although there were no symptoms. Because the technique of transatrial dilation is blind, it is difficult to prevent the complication of pulmonary embolism completely. However, if the procedure is performed cautiously, thrombus can be evacuated and gushed out through the atriotomy as it was in 7 patients in groups 1 and 2. Because this type of thrombus was just below the membrane in group 1 patients and may not be identified well by angiogram, it is dangerous to use percutaneous balloon catheter as a first procedure. In our hospital, we had one experience in using this technique to treat a patient who had membranous obstruction only in which the patient had cardiac arrest due to massive pulmonary emboli during cardiac catheterization and died. Whether infusion of urokinase to dissolve the thrombus before balloon dilation can effectively prevent this catastrophe requires further verification.

Table 2. Inferior Vena Cava to Right Atrium Pressure Gradient (mm Hg)

Patient No.	Preoperative	Postoperative
1	12	2
2	16	4
3	22	0
4	12	2
5	17	0
6	15	4
7	14	2
8	19	2
9	18	4
10	17	2
11[a]	18	4

[a] Required second operation 8 months after first operation, and then repeated balloon dilation.

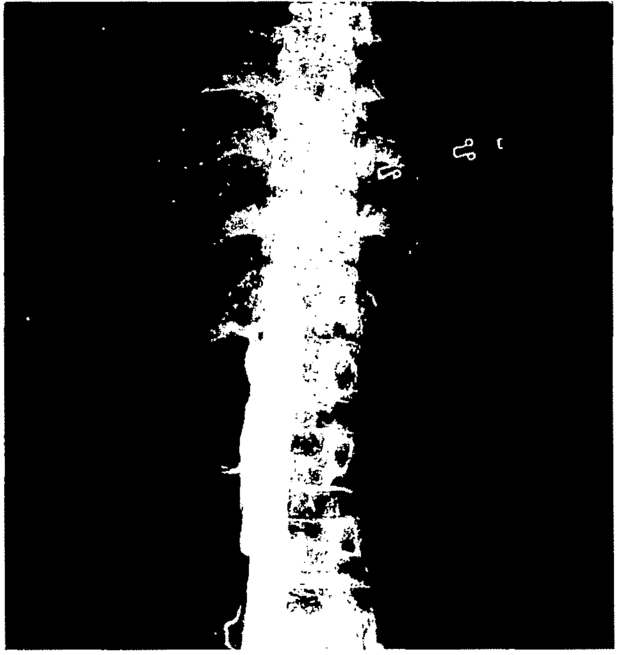

Fig 1. Inferior venacavogram in patient with membranous obstruction and long-segment thrombosis.

Other techniques, such as use of deep hypothermia and circulatory arrest to perform thrombectomy and correct IVC stricture under direct vision, were suggested by Murphy and colleagues [14]. However, deep hypothermia and circulatory arrest is not without complications in these critically ill patients [19]. This radical technique may be reserved for group 3 patients with long segments of IVC obstruction (Fig 1) because group 3 patients treated with transatrial membranotomy did not achieve the excellent results of patients in groups 1 and 2. However, more experience with this radical technique is needed to justify its superiority to transatrial membranotomy. For patients in groups 1 and 2, transatrial membranotomy can achieve an excellent immediate and long-term postoperative result.

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Long-Term Results After Surgical Repair of Incomplete Endocardial Cushion Defects

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Since 1964, 56 children (mean age, 6.7 years) underwent repair of incomplete endocardial cushion defects. Forty patients had isolated ostium primum defects. Additional congenital defects were present in 17 patients (30%). All patients underwent patch closure of the ostium primum defect and 47 of 56 patients (84%) underwent mitral valvuloplasty. Hospital mortality was 1.8% (one death). Arrhythmias developed in 7 other patients in the early postoperative period, of which six were transient and resolved completely. One patient required early pacemaker placement for complete heart block. Cumulative follow-up was 378 patient-years. There were three late deaths (5.7%), and additional operations were required in 12 patients (22.6%). Seven of these 12 patients required mitral valve replacement for severe mitral regurgitation. The mean interval between initial repair and mitral valve replacement was 4.2 years, with only three valves needing replacement within 12 months. There was a significant correlation between the severity of mitral regurgitation before initial repair and subsequent need for mitral valve replacement. Late onset atrial arrhythmias have developed in 6 patients. Current functional status has been evaluated in 50 of 52 surviving patients and 88.5% are in NYHA class I, with the remainder in class II.

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Incomplete endocardial cushion defects (partial atrioventricular canal defects) are characterized anatomically by the presence of an ostium primum atrial septal defect and two separate atrioventricular valves that are fused to the somewhat deficient crest of the interventricular septum. Varying degrees of clefting of the anterior leaflet of the mitral valve and deficiency of the septal leaflet of the tricuspid valve are also present.

Because several investigators have reported excellent short-term results of repair of incomplete endocardial cushion defects, this study evaluates the late results of surgical repair and defines an important prognostic factor influencing the need for reoperation [1–4].

Patients and Methods

From 1964 to 1986, 56 children underwent surgical repair of incomplete endocardial cushion defects at Children's Hospital National Medical Center. Age of operation ranged from 10 months to 19 years (mean age, 6.7 years) (Table 1). There were 30 female and 26 male patients. Associated cardiovascular anomalies were present in 17 of 56 patients (30%) and are listed in Table 2. Four patients had Down's syndrome, 1 had CHARGE association (coloboma, congenital heart disease, and choanal atresia with multiple anomalies) [5], and 1 had fetal alcohol syndrome.

All patients underwent preoperative cardiac catheterization to establish the diagnosis, assess mitral valve function, and calculate pulmonary vascular resistance. The diagnosis of incomplete endocardial cushion defect was correctly established by catheterization in 54 of 56 patients (96.4%). Two patients diagnosed as having complete endocardial cushion defects preoperatively were found to have incomplete defects at the time of surgical repair. Mitral regurgitation, as defined by cineangiographic criteria, was severe in 5 patients (8.9%), moderate in 13 (23.2%), and mild in 28 (50%). No mitral regurgitation was demonstrated in 7 patients (12.5%) and valve competence could not be adequately assessed in 3 patients (5.4%).

Mean pulmonary artery pressures ranged from 7 to 42 mm Hg (mean, 20 mm Hg) and pulmonary to systemic flow ratios (Q_p/Q_s) ranged from 1.6 to 5.6 (mean, 2.8). Pulmonary vascular resistance was calculated in 52 patients and ranged from 0.3 to 4.3 Woods units (mean, 1.2 Woods units). Pulmonary resistance at catheterization exceeded 4.0 Woods units in only 1 patient (4.3 Woods units), and this value decreased to 1.9 Woods units with the administration of 100% oxygen and Priscoline (tolazine hydrochloride) (ie, the patient had labile pulmonary hypertension).

Indications for operative intervention included a Q_p/Q_s ratio greater than 1.5, the presence of severe mitral regurgitation, and increasing pulmonary vascular resistance. Recommended age for surgical correction for incomplete endocardial cushion defects is 4 years, with earlier operation for failure to thrive or the presence of congestive heart failure poorly controlled by medical therapy.

Operative repair was accomplished using total cardiopulmonary bypass under moderate hypothermia (perfusate temperature, 25° to 28°C) with aortic cross-clamping and cardioplegia administration. The cleft in the anterior

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Table 1. Age at Repair of Incomplete Endocardial Cushion Defects

Age (yr)	No. of Patients	%
0–1	2	3.6
1–3	5	8.9
3–6	29	51.8
6–10	10	17.9
10–15	6	10.7
15	4	7.1
Total	56	100

leaflet of the mitral valve was closed with interrupted suture technique in 47 patients (84%). The ostium primum atrial septal defects were repaired with patches of prosthetic material in 50 patients, Dacron in 21, Teflon in 29, and autologous pericardium in 6. In no patient was the defect repaired primarily. Interrupted horizontal mattress sutures were used to approximate the patch to the mitral side of the annular tissue between the two atrioventricular valves. A continuous suture was then used for the remainder of the repair, taking care to deviate this suture line toward the left atrial side of the interatrial septum inferiorly to avoid injury to the conduction system. The coronary sinus was thus allowed to drain physiologically into the right atrium.

Results

Early postoperative complications occurred in 16 patients (28.6%) and are listed in Table 3. There was one hospital death representing a mortality of 1.8%. This early death was related to postoperative third-degree heart block associated with acute left ventricular failure. Arrhythmias developed in 7 other patients after surgical repair. In 6 of these 7 patients the arrhythmia was transient in nature and resolved completely. Three of these 6 patients exhibited junctional tachyarrhythmias, and the remaining 3 had variable degrees of atrioventricular block. One patient required early permanent pacemaker placement for persistent complete heart block. Postpericardiotomy syndrome occurred in 3 patients, pleural effusion in 2, and congestive heart failure requiring inotropic support in 2. One patient received a full course of antimicrobial therapy for sepsis. Forty patients (71%) had no early complication after surgical repair.

Table 2. Cardiovascular Anomalies Associated With Incomplete Endocardial Cushion Defects

Anomaly	Occurrence (No. of Defects)[a]	Percentage of Total
Patent foramen ovale	6	27.3
Secundum atrial septal defect	5	22.7
Pulmonary valvar stenosis	3	14.0
Patent ductus arteriosus	2	9.0
Anomalous pulmonary venous return	1	4.5
Subaortic membrane	1	4.5
Coarctation of aorta	1	4.5
Left superior vena cava	1	4.5
Polysplenia syndrome	1	4.5
Absent inferior vena cava with azygous continuation	1	4.5

[a] Twenty-two total defects in 17 patients.

Table 3. Early Postoperative Complications After Repair of Incomplete Endocardial Cushion Defects

Complication	No. of Patients	%
Death	1	1.8
Arrhythmia		
Transient	6	10.7
Persistent	1	1.8
Postpericardiotomy syndrome	3	5.3
Pleural effusion	2	3.6
Congestive heart failure	2	3.6
Sepsis	1	1.8
None	40	71.4
Total	56	100.0

Follow-up evaluation was performed in 53 of 55 survivors with a range of 1 year to more than 19 years (mean follow-up, 7 years). Results of long-term follow-up are listed in Table 4. There were three late deaths (5.7%). One patient died of acquired immunodeficiency syndrome presumed to be acquired from perioperative blood transfusions more than 6 years after surgical repair. A second patient died of left ventricular failure after a second mitral valve replacement 8 months after initial repair. A third patient, with previously repaired total anomalous pulmonary venous drainage, died 10 months after initial repair of a refractory ventricular tachyarrhythmia after pneumonectomy for recurrent pulmonary venous stenosis that was unrepairable surgically. Actuarial survival is shown in Figure 1.

Additional operations were performed in 12 patients (22.6%). Although no patient underwent mitral valve

Table 4. Long-Term Results After Repair of Incomplete Endocardial Cushion Defects

Long-Term Result	No. of Patients	%
Late death	3	5.7
Reoperation	12	22.6
Late arrythmia[a]	6	11.3
Residual lesion[b]	6	11.3

[a] Onset more than 30 days after initial repair. [b] Atrial septal defect, moderate to severe mitral regurgitation.

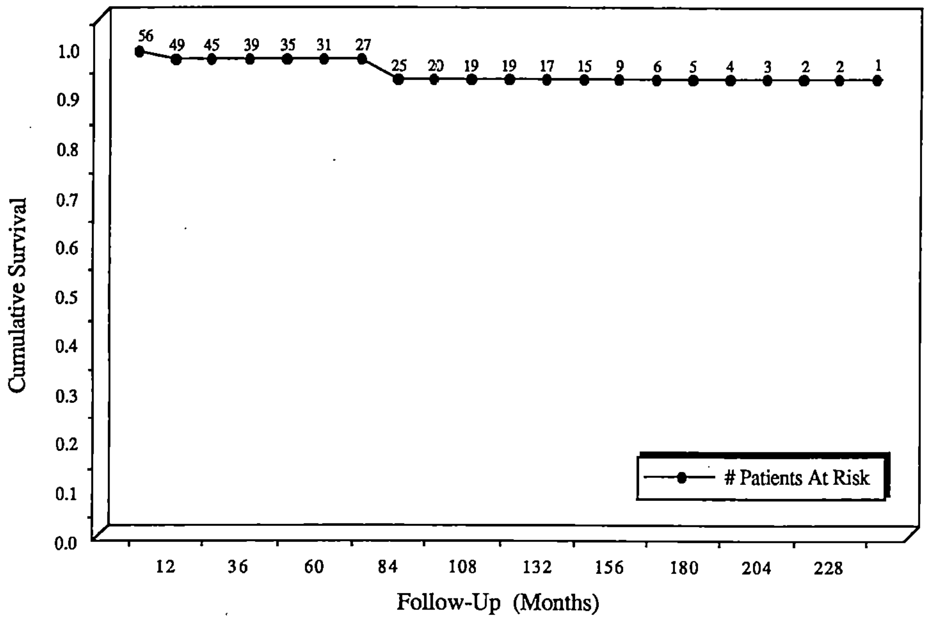

Fig 1. Cumulative survival curve after initial repair of incomplete endocardial cushion defects.

replacement at the time of initial repair, 7 patients subsequently required mitral valve replacement for severe mitral regurgitation. All 7 patients had closure of the mitral cleft at the time of original repair. The mean interval between initial repair and the first mitral valve replacement was 4.2 years (range, 1 month to 10 years 5 months). There were no deaths associated with first mitral valve replacement. Three patients required mitral valve replacement within 12 months of the initial operation (1, 2, and 10 months). The first of these patients had no clinically significant mitral regurgitation preoperatively. Progressive mitral incompetence postoperatively was associated with a residual atrial septal defect. Early progressive mitral valve dysfunction also occurred in the second patient associated with distortion of the mitral valve chordae noted at reoperation. Annular dilatation was reported in the third patient.

Type of prosthetic valves used for initial mitral valve replacement were three Hancock (25, 25, and 29 mm), two Ionescu-Shiley (19 and 21 mm), 1 St. Jude (27 mm), and 1 Björk-Shiley (27 mm). Neither mechanical valve has required replacement to date. All prosthetic tissue valves have required replacement for prosthetic valve stenosis. The mean interval between first and second mitral valve replacements was 4.8 years (range, 7 months to 8 years 2 months), and there was one death associated with second mitral valve replacement. Of prognostic significance, 71.4% of all patients requiring initial mitral valve replacement had moderate to severe mitral regurgitation defined by cineangiography before repair of their incomplete endocardial cushion defects. Only 2 of 35 patients (5.7%) with mild or absent mitral regurgitation present preoperatively required subsequent mitral valve replacement ($p = 0.0375$).

Residual atrial septal defects were demonstrated by follow-up catheterization in 3 patients. Pulmonary to systemic flow ratios in these patients ranged from 1.6 to 3.7. One of these patients also had severe mitral regurgitation and underwent mitral valve replacement along with repair of the residual atrial septal defect. A second patient underwent reoperation and patch closure of the recurrence, and the remaining patient has been followed clinically.

Clinically significant fibromembranous subaortic stenosis with resting peak systolic gradients of 40 and 60 mm Hg developed in 2 patients after repair of their incomplete endocardial cushion defects. In 1 patient, the subaortic membrane had been resected at initial repair and recurred 17 months later requiring a second resection. The second patient required resection 41 months after initial repair. Figure 2 shows actuarial survival free of reoperation.

Late onset atrial arrhythmias developed in 6 patients after initial repair. In 4 of these patients the arrhythmia has been intermittent atrial flutter/fibrillation controlled with medical therapy. One patient developed sick sinus syndrome 9 months after surgical repair and required placement of a permanent pacing system. One other patient required permanent pacing 10 years after initial repair for complete heart block after a second mitral valve replacement. No patient spontaneously developed late onset complete atrioventricular block.

Current functional status has been evaluated in 50 of 52 surviving patients (96%); 88.5% are currently in New York Heart Association class I and the remainder are in class II.

Comment

Our experience confirms that incomplete endocardial cushion defects can be repaired with low operative mortality and with a low incidence of conduction system injury.

Age, functional status, and degree of preoperative mitral regurgitation did not significantly affect hospital mortality. However, significant late morbidity has occurred in patients noted to have moderate to severe mitral incompetence before incomplete endocardial cushion de-

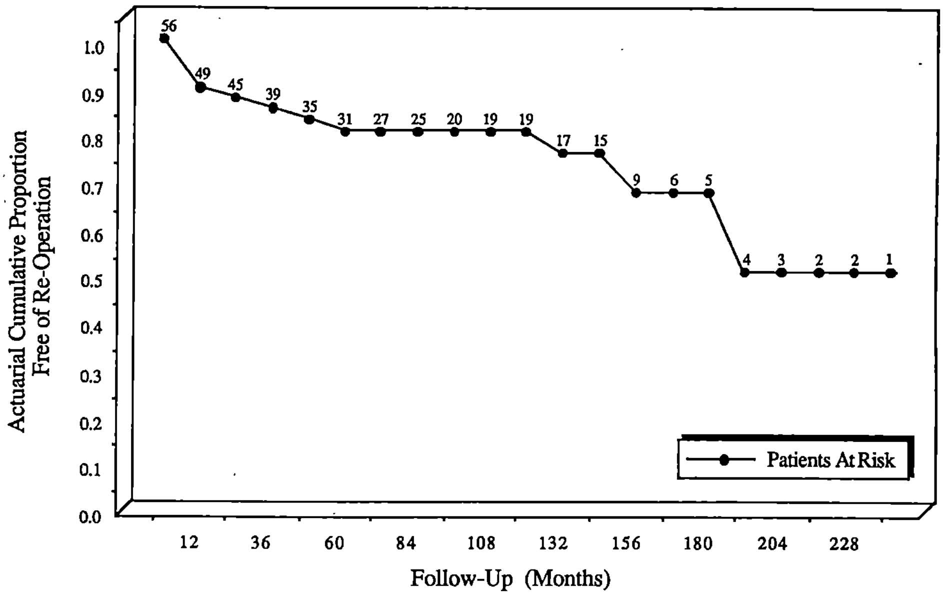

Fig 2. Cumulative proportion of patients free from reoperation after initial repair of incomplete endocardial cushion defects.

fect repair. Twenty-eight percent of patients in our series who demonstrated moderate to severe mitral regurgitation on preoperative cardiac catheterization ultimately required mitral valve replacement. This compares with a 5.7% incidence of mitral valve replacement in patients exhibiting only mild or absent mitral regurgitation preoperatively. In addition, of 4 patients with residual moderate to severe mitral incompetence after initial repair who have not required mitral valve replacement to date, 3 demonstrated clinically significant mitral incompetence before repair. The correlation between preoperative mitral valve function and postoperative morbidity also has been described in other series [1, 6]. Despite this correlation, we do not recommend mitral valve replacement at the time of initial repair. No patient in our series underwent mitral valve replacement coincident with initial repair, and the mean interval between initial repair and mitral valve replacement was 4.2 years.

Although current operative techniques have greatly reduced the incidence of surgically induced complete heart block associated with repair of incomplete endocardial cushion defects, postoperative arrhythmias are not uncommon. Our incidence of early postoperative arrhythmia was 12.5%, and late onset arrhythmias developed in another 11% of patients. However, no patient experienced spontaneous late onset complete heart block or sudden death.

In summary, progress has been made in reducing the operative mortality and incidence of perioperative heart block associated with repair of incomplete endocardial cushion defects. However, a sizeable incidence of long-term morbidity makes careful follow-up essential [7, 8].

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Surgical Preparation Impairs Release of Endothelium-Derived Relaxing Factor From Human Saphenous Vein

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Release of endothelium-derived relaxing factor was measured from freshly isolated human saphenous vein and from vein subject to routine surgical preparation for coronary artery bypass grafting. Surgical preparation led to a significant decline in endothelium-derived relaxing factor release as compared with freshly isolated vein, and these changes were associated with loss of endothelial coverage. Storage of freshly isolated vein in blood but not in Hartmann's solution also resulted in a decline in maximally stimulated endothelium-derived relaxing factor release that was not associated with loss of endothelium. Reduced production of endothelium-derived relaxing factor, a potent vasodilator and inhibitor of platelet adhesion and aggregation, may be implicated in the etiology of early vein graft thrombosis.

(Ann Thorac Surg 1989;48:417–20)

Coronary artery bypass grafting with autologous saphenous vein relieves symptoms, at least initially, in most patients and prolongs life in those with the most severe disease [1]. Graft occlusion occurs postoperatively, however, and perhaps as many as 15% of all grafts suffer thrombotic occlusion during the first 12 months [2, 3]. Subsequent failure occurs at a rate of 2% per year owing to accelerated myointimal hyperplasia with or without superimposed atheroma [2–4].

A series of well-defined pathological and degenerative changes occur in saphenous vein grafts during and after implantation [5–11]. Endothelial separation and partial desquamation occur during surgical preparation [7, 9], and the resulting exposure of collagen promotes platelet and fibrin attachment [9, 11]. Endothelial damage also reduces production of prostacyclin [5], a powerful inhibitor of platelet aggregation, and this further promotes platelet activation. Platelet activation may precipitate early thrombosis or lead to secretion of mitogens responsible for the rapid medial and neointimal proliferation that occurs in vein grafts during the first few months [9, 11].

The endothelium produces a second potent locally acting vasodilator substance known as endothelium-derived relaxing factor (EDRF). Release of EDRF mediates vascular relaxation tonically, in response to increased flow and also in response to a variety of agonists, some of which (eg, adenosine triphosphate, 5-hydroxytryptamine) may be released from activated platelets [12]. It has been recently demonstrated that EDRF is also a potent inhibitor of platelet aggregation and adhesion [12, 13]. Therefore, EDRF probably functions to limit vasoconstriction and thrombus propagation at sites of vascular injury. Loss of EDRF activity due to endothelial injury during preparation of saphenous vein for coronary bypass grafting might contribute to graft thrombosis.

We therefore investigated the influence of surgical preparation on the capacity of human saphenous vein to release ERDF.

Material and Methods

Endothelium-denuded porcine coronary artery (PCA) rings (2 to 3 mm wide) were mounted as recipients in a cascade bioassay system as previously described [14]. They were perfused at a flow rate of 2 mL/min with prewarmed (37°C), gassed (95% O_2, 5% CO_2) Holman's solution of the following composition (in mM): NaCl, 120; KCl, 5; NaH_2PO_4, 1.3; $NaHCO_3$, 25; $CaCl_2$, 2.5; D-glucose, 11; and sucrose, 10. The Holman's solution also contained the cyclooxygenase inhibitor indomethacin (10 μM) to prevent synthesis of prostanoids.

All rings were tested for successful removal of endothelium by preconstriction with 5-hydroxytryptamine (5HT, 10 μM) and brief (one minute) exposure to an EDRF-releasing agent, the calcium ionophore A23187 (0.1 μM). Any rings showing a relaxant response to A23187 were considered to have some functional endothelium and discarded.

Vein was obtained from patients undergoing coronary artery bypass grafting. Premedication, anesthesia, and intraoperative heparinization were standardized as detailed previously [6]. A segment (~2 to 3 cm) was taken from the lower portion of the long saphenous vein using a no-touch technique [15] as soon as possible after the first incision. This freshly isolated vein was brought to the laboratory in a tightly closed plastic universal container (capacity, 25 mL) in 20 mL of either patient's heparinized arterial whole blood (3 mg/kg patient body weight) or heparinized Hartmann's solution (4 μM/mL) and assayed for EDRF release within 60 minutes of removal.

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Table 1. Number, Age, and Sex of Patients From Whom Veins Were Removed and Storage Time for Each Group

Vein	n (Sex)	Age (yr)	Storage Time (min)
Freshly isolated (blood)	4 (2 male)	55 ± 4	36 ± 9
Freshly isolated (Hartmann's solution)	4 (2 male)	56 ± 5	25 ± 5
Stored (blood)	6 (all male)	56 ± 2	125 ± 11
Stored (Hartmann's solution)	7 (6 male)	58 ± 2	160 ± 23
Surgically prepared	11 (9 male)	59 ± 2	124 ± 11
Surgically prepared (Hartmann's solution)	8 (7 male)	50 ± 2	191 ± 12

When applicable, data are shown as mean ± standard error of the mean.

Surgically prepared vein was obtained from vein in excess on completion of the last proximal anastomosis. Routine preparation consisted of adventitial stripping, side branch ligation, uncontrolled manual distention, and storage at room temperature either in heparinized arterial whole blood or heparinized Hartmann's solution. In some experiments, freshly isolated veins were stored in the collecting media for up to 250 minutes at room temperature (23°C). The characteristics of the different vein preparations are shown in Table 1.

A 2-cm length of saphenous vein was mounted in the bioassay and used as a donor vessel for EDRF. Basal EDRF and EDRF release in response to cumulative doses of bradykinin (1 nM to 1 μM) were measured [16]. Maximum EDRF release was induced by the calcium ionophore A23187 (1 μM), a potent EDRF-releasing agent in human vessels [17]. In some experiments, the EDRF inhibitor hemoglobin [18] was added to the infusion to ensure that relaxation responses were EDRF mediated. Donor vessel endothelial cell loss during perfusion was estimated at the end of the experiment by en face silver staining [19] and light microscopy.

Rings of PCA were preconstricted to about 95% of maximum by 5HT (3 μM) infused postdonor using an LKB (type 2132) peristaltic pump. Porcine coronary artery responses were detected by an isometric force transducer (Ether type UF1 4 ounce) and displayed on a Devices chart recorder. Responses to EDRF are expressed as a percentage of the initial 5HT-induced tone, which was not altered by bradykinin or A23187 alone.

Drugs Used

5-Hydroxytryptamine (creatinine sulfate complex), bradykinin (acetate salt), indomethacin, hemoglobin (bovine), and A23187 (mixed Ca^{2+}, Mg^{2+} salt) were purchased from the Sigma Co Ltd, Poole, UK. Stock solutions of indomethacin (10 mM) and A23187 (5 mM) were made up in 99% ethanol and dimethylsulfoxide, respectively. Bradykinin and 5HT were dissolved in distilled water. Final concentrations of ethanol and dimethylsulfoxide did not affect tissue responses in this system. The source of other materials was described previously [10].

Statistical Analysis

Concentration–response curve slopes and EC_{50} values for bradykinin-induced EDRF release were calculated from a line fitted to the straight part of the concentration–response curve by a least-squared minimization procedure. Results were compared using Student's t test for unpaired data and were considered significantly different at $p < 0.05$. Data were presented as mean ± standard error of the mean.

Results

Responses to Endothelium-Derived Relaxing Factor

A representative trace recorded from a PCA ring preconstricted with 5HT (3 μM) is shown in Fig 1. Perfusion through saphenous vein causes a small relaxation of the PCA due to basal EDRF release. Bradykinin added predonor caused a dose-dependent relaxation of the PCA. Maximum EDRF release is induced by the calcium ionophore A23187 (1 μM). Relaxations were completely reversed by hemoglobin (10 μM) and by removal of endothelium from the vein, confirming that the relaxations were EDRF mediated. For the purpose of this study, relaxation mediated by bradykinin-induced EDRF release was taken as bradykinin-induced relaxation minus basal relaxation, and maximum A23187-induced relaxation as basal relaxation plus bradykinin-induced relaxation plus A23187-induced relaxation.

Endothelium-Derived Relaxing Factor Release

Maximum A23187-induced release proved the best predictor of functional endothelial integrity, as responses to bradykinin varied greatly. The results for maximum release are shown in Fig 2.

FRESHLY ISOLATED (BLOOD). Basal and maximally stimulated EDRF release from freshly isolated veins collected in blood caused 18% ± 5% and 48% ± 3% relaxation, respectively, of PCA rings preconstricted to 9.7 ± 0.8 g tension with 5HT. The EC_{50} for bradykinin was 16.6 ± 9.8 nM, and the concentration–response curve slope was 5.2 ± 1.4.

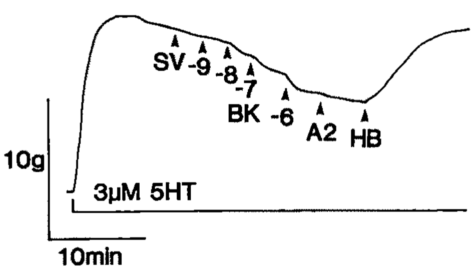

Fig 1. A representative trace from an experiment showing endothelium-derived relaxing factor (EDRF)-induced relaxation in an endothelium-denuded porcine coronary artery ring preconstricted with 3 μM 5-hydroxytryptamine (5HT). Introduction of the donor vessel into the system (SV) caused a small relaxation due to basal EDRF release. Further EDRF release from the donor vessel was induced by cumulative addition of bradykinin (BK, 1 nM to 1 μM) followed by A23187 (A2, 1 μM). Addition of hemoglobin (HB, 10 μM) completely inhibited this relaxation.

FRESHLY ISOLATED (HARTMANN'S). Basal and maximally stimulated EDRF release from freshly isolated veins collected in Hartmann's solution caused 8% ± 3% and 42% ± 3% relaxation, respectively, of PCA rings preconstricted to 8.4 ± 0.6 g tension with 5HT. The EC_{50} value for bradykinin was 45.7 ± 13.2 nM, and the concentration–response curve slope was 6.3 ± 0.6.

STORED (BLOOD). Basal and maximally stimulated EDRF release from veins stored in blood caused 8% ± 1% and 26% ± 4% relaxation, respectively, of PCA rings preconstricted to 8.1 ± 0.7 g tension with 5HT. Basal and maximum release was significantly less than that of freshly isolated veins collected in blood ($p < 0.05$). The EC_{50} value for bradykinin was 11.3 ± 1.9 nM, and the concentration–response curve slope was 5.5 ± 1.14.

STORED (HARTMANN'S). Basal and maximally stimulated EDRF release from veins stored in Hartmann's solution caused 8% ± 3% and 42% ± 3% relaxation, respectively, of PCA rings preconstricted to 8.5 ± 0.6 g tension with 5HT. Basal and maximum EDRF release was not significantly different from that of freshly isolated veins collected in Hartmann's solution. The EC_{50} value for bradykinin was 24.6 ± 5.5 nM, and the concentration–response curve slope was 7.3 ± 1.1.

SURGICALLY PREPARED (BLOOD). Basal and maximally stimulated EDRF release from surgically prepared veins using blood caused 6% ± 1% and 19% ± 2% relaxation, respectively, of PCA rings preconstricted to 7.5 ± 0.2 g tension by 5HT. Basal and maximum EDRF release was significantly less than that of freshly isolated vein collected in blood ($p < 0.01$) but not significantly different from that of blood-stored veins. The EC_{50} value for bradykinin was 10.8 ± 3.2 nM, and the concentration–response curve slope was 2.8 ± 0.4. The bradykinin concentration–response curve was significantly less steep than that of blood-stored veins ($p < 0.05$).

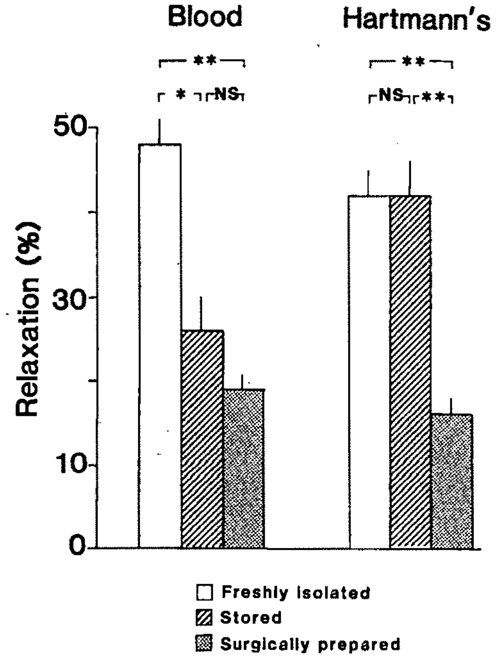

*Fig 2. Percentage of relaxation of 5-hydroxytryptamine–preconstricted porcine coronary artery rings in response to maximum A23187-induced endothelium-derived relaxing factor release from freshly isolated, stored, and surgically prepared saphenous veins. Data are shown for veins collected and stored in blood or Hartmann's solution, as detailed in text. (NS = not significant; *p < 0.05, **p < 0.01.)*

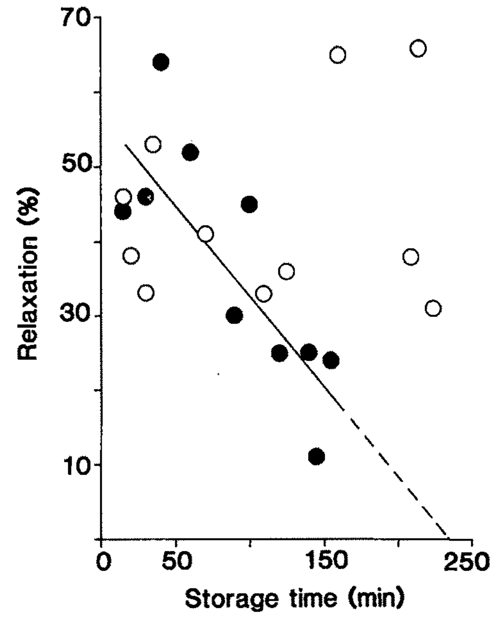

Fig 3. Decline of maximum A23187-induced endothelium-derived relaxing factor release from freshly isolated veins stored in blood or Hartmann's solution. Endothelium-derived relaxing factor release is expressed as percentage of relaxation of 5-hydroxytryptamine–preconstricted porcine coronary artery rings. A regression line is fitted to the blood-stored data (r = 0.76, p < 0.05).

SURGICALLY PREPARED (HARTMANN'S). Basal and maximally stimulated EDRF release from surgically prepared veins using Hartmann's solution caused 5% ± 1% and 16% ± 2% relaxation, respectively, of PCA rings preconstricted to 7.5 ± 0.3 g with 5HT. Maximum EDRF release was significantly less than that of both veins stored in Hartmann's solution and freshly isolated veins collected in Hartmann's solution ($p < 0.01$). The EC_{50} value for bradykinin was 21.9 ± 8.8 nM, and the concentration–response curve slope was 2.9 ± 0.4. The bradykinin concentration–response curve slope was significantly less steep than that of veins stored in Hartmann's solution ($p < 0.01$).

Decline of Maximum Endothelium-Derived Relaxing Factor Release During Storage

The maximum EDRF release from veins stored for different lengths of time in blood (10 patients [2 women] aged 56 ± 2 years) and Hartmann's solution (11 patients [1 woman] aged 58 ± 2 years) is shown in Figure 3. Porcine coronary artery rings were preconstricted to 8.8 ± 0.6 and 8.5 ± 0.4 g tension, respectively. A regression line fitted to data obtained from the veins stored in blood at room temperature ($r = 0.76$) described a straight line ($p < 0.05$), indicating that EDRF release declined to zero after storage for 236 minutes. A regression line fitted to the data obtained from the veins stored in Hartmann's solution at room temperature, however, had a low correlation coefficient ($r = 0.05$), indicating that maximum EDRF release did not decline as a result of storage in this medium.

Endothelial Preservation

Representative veins taken from the freshly isolated groups showed more than 70% endothelium coverage, which was not altered by storage in either blood or Hartmann's solution. Routine surgical preparation, however, reduced endothelium coverage to about 30%, consistent with the results of our previous study [5].

Comment

To investigate the influence of surgical preparation on release of EDRF from human saphenous veins, we used a bioassay cascade rather than relaxation of vascular rings [16, 20]. This was because during removal and preparation of saphenous vein for coronary artery bypass grafting, metabolic changes that occur in medial smooth muscle cells [5, 6, 11] may alter their responsiveness to EDRF. Our study demonstrated release of EDRF from freshly isolated saphenous vein (which had more than 70% endothelial coverage) and confirmed the presence of responses to both bradykinin [16] and the calcium ionophore A23187 [17, 20]. The principal finding of this study was that EDRF release was reduced by routine surgical preparation. Indeed, the approximate 70% of endothelial loss correlated with the 60% reduction in EDRF release. This finding is in agreement with results of our previous study [5], in which an approximate 55% endothelial loss was accompanied by a 60% reduction in stimulated prostacyclin release after surgical preparation of human saphenous vein.

Storage of freshly isolated vein in blood also caused a time-related reduction in maximal EDRF release that was not observed in veins stored in Hartmann's solution. Because further loss of endothelium was not observed during storage, in blood the reduced release observed after blood storage may be attributed to an impaired ability of the endothelium to produce or release EDRF.

Because EDRF is an inhibitor of both platelet activation [13] and adhesion [12], reduced EDRF release may be implicated in early vein graft failure. These observations, therefore, provide further support for use of surgical techniques [7, 10, 15] designed to implant saphenous vein grafts with a metabolically preserved endothelium.

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Resection of Atriocaval Adrenal Carcinoma Using Hypothermic Circulatory Arrest

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Carcinoma of the adrenal cortex may occasionally extend through the inferior vena cava to the right atrium without actually invading the vascular endothelium. Surgical resection may result in excellent palliation and the potential for prolonged survival when no other signs of advanced disease are present. Extrapolating from our experience with renal cell carcinoma extending to the right atrium, we resected a similar adrenocortical carcinoma using hypothermic circulatory arrest.

(Ann Thorac Surg 1989;48:421–2)

We recently treated a patient with adrenocortical carcinoma involving the inferior vena cava, hepatic veins, and right atrium using hypothermic total circulatory arrest. To our knowledge, this is the first such case reported in the literature.

A 51-year-old woman was seen with a 3-month history of progressive weakness, fatigue, dyspnea, early satiety, ascites, and peripheral edema. Computed tomography showed a 12-cm right adrenal tumor with central necrosis and extension to the inferior vena cava (Fig 1). Inferior venacavography showed occlusion of the inferior vena cava and hepatic veins and enlarged azygos and hemiazygos collateral vessels. Superior venacavography demonstrated extension of tumor or clot to the right atrium. Evaluation for distant metastatic disease was unrevealing. Serum lactate dehydrogenase level was elevated (535 IU/L; normal, 124 to 275 IU/L).

Electroencephalographic leads were applied preoperatively. Abdominal exploration through a bilateral subcostal excision revealed that the adrenal tumor could be mobilized and had not invaded contiguous structures or nodes. Sternotomy was then performed.

Extracorporeal circulation was instituted, and sodium thiopental (Pentothal), 60 mg/kg, was administered. When body temperature reached 28°C during hypothermic cardiopulmonary bypass, the ascending aorta was cross-clamped, and cardiac arrest was induced by cold blood cardioplegia. Ice bags were applied to the head. Cardiopulmonary bypass was discontinued when rectal and nasopharyngeal temperature reached 16° to 18°C, and the patient's blood volume was partially exsanguinated into the cardiotomy reservoir. The right atrium and inferior vena cava at the level of the adrenal vein were opened. In a completely bloodless operative field, thrombus was extracted under direct vision from the right atrium, occluded hepatic veins, and vena cava. No endothelial invasion was noted. The excised tumor showed areas of necrosis, but no viable tumor cells were found in thrombus extracted from the hepatic veins. No tumor cells were found in the abdominal lymph nodes.

The period of total circulatory arrest was 18 minutes. Bypass was restarted after removal of tumor and vascular isolation of the upper inferior vena cava. The atriotomy was closed, and air was evacuated by backbleeding. The caval defect was reconstructed with a Gore-Tex patch while the patient was slowly rewarmed at a rate of no more than 1°C per three minutes. The aortic clamp was released, and the patient was defibrillated easily at a body temperature of 32°C.

The patient required vascular support with Neo-Synephrine (phenylephrine hydrochloride) and dopamine after operation. She awoke nine hours after the 10.5-hour procedure and was extubated on postoperative day 3. An estimated blood loss of 11 L and urinary output

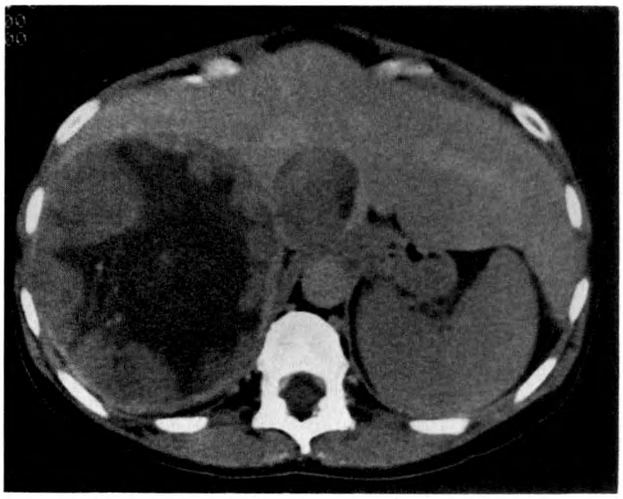

Fig 1. Computed tomographic scan of the abdomen demonstrates large right adrenal tumor displacing liver anteriorly. Tumor appears encapsulated. Adrenal vein and inferior vena cava are enlarged and filled with tumor thrombus. The liver and abdominal lymph nodes appear free of tumor.

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of 5.8 L were replaced with 12 L of a balanced salt solution, 15 units of packed red blood cells, 1.5 L of autologous blood aspirated after tumor removal, 4 units of fresh frozen plasma, and 10 units of platelets. The patient is well with mild dyspnea and a paretic right hemidiaphragm 10 months after operation.

Comment

The use of hypothermic circulatory arrest has not resulted in neurological or other adverse sequelae in the patient described here or in 6 other patients with atriocaval hypernephromas operated on using the same technique. Total circulatory arrest has been used only for that brief but critical interval required for precise tumor removal from the inferior vena cava, hepatic veins, and right atrium. Local caval control proximal and distal to the cavotomy site is then obtained, and bypass is reinstituted during caval reconstruction. Too few patients have undergone resection of adrenal tumors extending to the inferior vena cava to permit determination of actuarial survival. However, short-term survival of 5 to 22 months has been reported for patients who survived the procedure [1–6]; metastatic disease has developed in some of these patients. Of the 3 patients with tumors resected from the right atrium, 1 patient described by Hugh and colleagues [1] died of pulmonary metastasis 14 months after operation, whereas the second patient, whose tumor was resected using cardiopulmonary bypass, has remained free of disease at 15 months. The patient of Javadpour and colleagues [6] was reported to be free of disease 12 months after operation.

We advocate radical one-stage resection of adrenal tumors extending to the inferior vena cava and right atrium provided no other evidence of disseminated local or systemic disease is present. Hypothermic circulatory arrest can be performed safely and provides superior visualization and complete removal of intracaval, hepatic vein, and right atrial tumors.

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Combined Gastric Pull-up and Microvascular Jejunal Transfer Procedure After Pharyngolaryngoesophagectomy

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A case of simultaneous carcinomas of the lower thoracic esophagus and the oropharynx in a 62-year-old man is reported. Reconstruction was successfully performed using a one-stage operation consisting of pharyngolaryngoesophagectomy followed by a combination of gastric pull-up and microvascular jejunal transfer procedures. The postoperative course was uneventful except for regurgitation of food, which persisted for 1 month.

(Ann Thorac Surg 1989;48:423–5)

Reconstruction after resection of the pharyngoesophageal area has been one of the most difficult problems in surgery. We report a new one-stage reconstructive procedure using gastric pull-up and microvascular jejunal transfer after pharyngolaryngoesophagectomy. The operative procedure and its usefulness are described in detail.

A 62-year-old man, complaining of dysphagia for 1 month, was examined at the National Cancer Center Hospital. He had two separate malignancies, squamous cell carcinomas in the lower thoracic esophagus and the oropharynx, the latter extending from the left tonsil and base of the tongue orally to the pharyngoepiglottic fold distally. The following operative procedure was devised to resect these two remote lesions and to reconstruct the defect simultaneously.

First, through a fifth intercostal posterolateral incision, the esophagus was dissected free of the mediastinal structures along the full length in the thorax, and lymph nodes were dissected extensively. After closure of the chest, the following procedures were performed simultaneously by two separate teams. Through the upper median laparotomy incision, mobilization of the stomach, pericardiac dissection, and pyloroplasty were accomplished, preserving the right gastric and the right gastroepiploic vessels as well as the gastroepiploic arcade. In the neck, a left radical neck dissection was performed first; an en bloc resection of the base of the tongue, left tonsil, pharynx, larynx, and left lobe of the thyroid was then performed, preserving continuity of the esophagus. Then the entire thoracic esophagus was drawn up through the thoracic inlet by upward traction, followed by the stomach. The gastroesophageal junction, now in the neck, was divided and stapled with a gastrointestinal anastomosis instrument and oversewn. Because the defect in the cervical esophagus was too large to be reconstructed by only a pedicled stomach transfer, a free jejunal interposition graft between the oropharynx and the pull-up stomach was planned.

Because of the extremely enlarged pharyngeal stoma, a doubly looped jejunal segment was placed between the pharyngeal stoma and the stoma created at the fornix of the pull-up stomach. A longitudinal incision, about 5 cm long, was made at the central portion of the harvested jejunal segment, about 30 cm long. The jejunal segment was then folded to create the doubly looped segment, of which the central stoma was anastomosed to the pharyngeal stoma and the distal jejunal stumps were anastomosed to the stoma created at the fornix (Fig 1). By microvascular technique, the mesenteric artery and vein of the jejunal graft were also anastomosed to the transverse cervical artery and external jugular vein, respectively (Fig 2).

After a tracheostoma was made, the cervical wound was closed with two drains left at the anastomoses. As the surgical margin of the resected specimen, especially the proximal margin at the left tonsil, was macroscopically very close to the border of the carcinomatous involvement, postoperative irradiation at a total dose of 50 Gy was performed despite the lack of microscopic evidence of cancer exposure.

Fluoroscopy on the twelfth postoperative day revealed no anastomotic leakage, and oral intake was started. The patient suffered from regurgitation for 1 month and required parenteral nutritional support. This symptom, however, gradually improved and completely disappeared by the end of the third month after operation. Nasal reflux never occurred.

Comment

A patient with one epidermoid carcinoma in the upper digestive system, larynx, or lung has an increased risk of developing a new cancer at the same subsite or at another site within these systems [1]. According to previous reports, multiple primary cancer develops in 10% to 30% of patients with head and neck cancer [2–4]. Therefore, as

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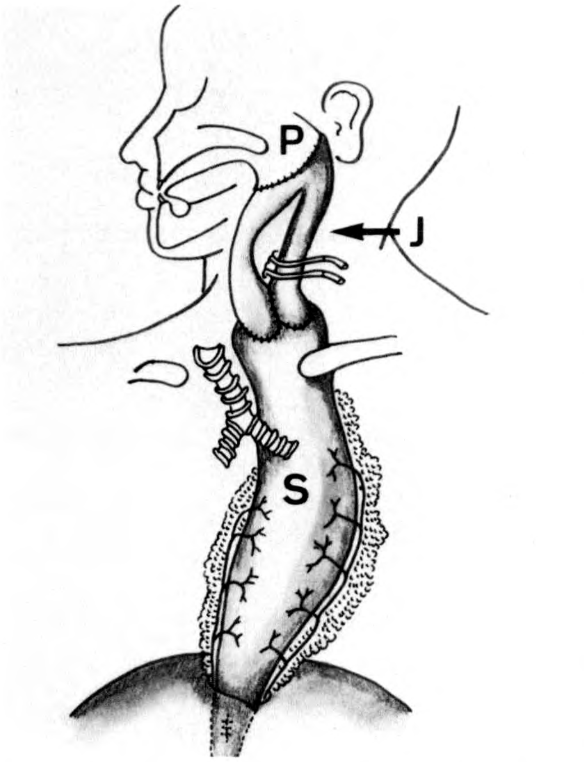

Fig 1. Reconstructive procedure. A free jejunal autograft (J) was interposed between the pull-up stomach (S) and the oropharynx (P). The stomach was pulled up through the posterior mediastinal route.

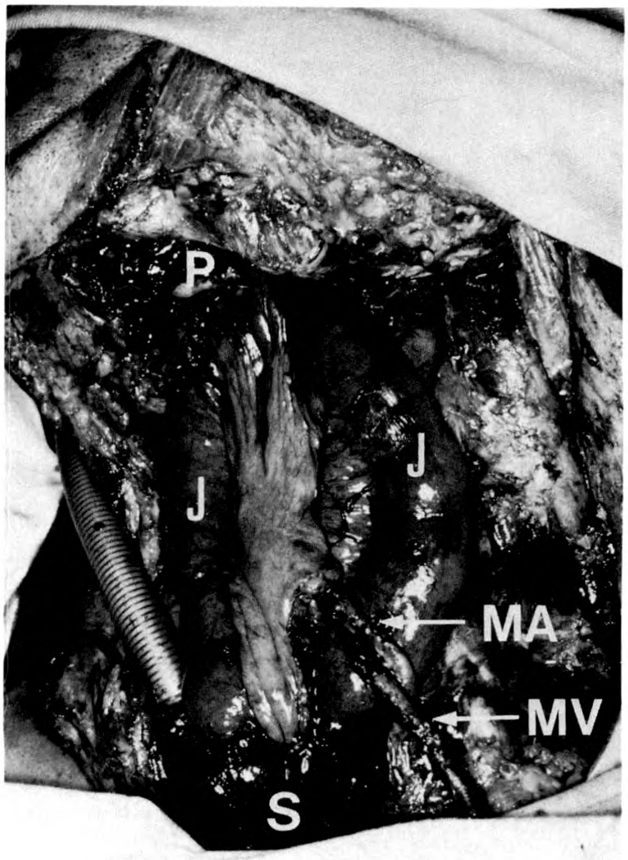

Fig 2. Operative field in the neck after the reconstruction was completed. As a doubly looped jejunal tract, a free jejunal autograft (J) was interposed between the oropharynx (P) and the stomach (S), which was pulled up through the posterior mediastinal route. The mesenteric artery (MA) and vein (MV) were anastomosed by a microvascular technique to the transverse cervical artery and external jugular vein, respectively.

in the present case, a vigorous survey of the upper aerodigestive system is indispensable in treating a patient with malignancy of one of these systems to avoid overlooking a latent malignancy.

Methods used clinically for replacement of the pharynx and cervical esophagus may be classified under three major categories: local measures with pharyngolaryngeal tissues, cutaneous methods including skin or musculocutaneous flaps, and visceral methods with a pedicled or revascularized free autograft [5]. In 66 cases, we compared three methods for reconstruction of the hypopharynx and cervical esophagus: a free forearm skin tube flap, free jejunal transfer, and pharyngogastric anastomosis after pull-through esophagectomy [6]. The clinical outcome was as follows: The free forearm skin tube was the safest of the three methods, but it could be used for a short defect only, and a higher incidence of salivary fistula (50%) was noted. Despite having the highest incidence of complications, the pull-through esophagectomy guaranteed a safe surgical margin and was useful for a long reconstruction. The free jejunal transfer could be applied to defects of various lengths with less operative burden and less frequent complications.

The present case was peculiar in two points: the extremely long defect due to total esophagectomy and the irregular shape of the pharyngeal stoma. Apart from the present method, a pedicled long colon transposition graft might have been used alternatively in this situation. That method, however, may be inferior to the present method using a doubly looped jejunal segment in ease of anastomosis at the pharyngeal stoma because of its irregularly enlarged shape. We believe that our present technique can be used when the more conventional procedures are not available and, in addition, has the advantage of being a one-stage operation.

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REVIEW OF RECENT BOOKS

Coronary Angioplasty
Edited by Sheldon Goldberg, MD
Philadelphia, F.A. Davis Company, 1988
285 pp, illustrated

Reviewed by Laurence H. Coffin, MD

This work represents the nineteenth volume of Cardiovascular Clinics, with Albert N. Brest as Editor-in-Chief. It is divided into part I: Performance of Angioplasty; part II: Angioplasty in Specific Patient Populations; and part III: Complications of Angioplasty. Of the fifteen chapters, all but one are written by cardiologists. Surgeons Mannion and Edie are given the opportunity to bat in the "cleanup position" and as such exert a balancing effect on the unbridled enthusiasm of cardiologists who have never manually dealt with small atherosclerotic coronary arteries and do not appreciate the unforgiving response of these tissues to mechanical insults.

Outstanding in part I are the chapters on adjunctive pharmacologic treatment, which review antithrombotic, antispastic, and other maneuvers to minimize the angioplasty-induced vascular injury, as well as the chapters on protection of the ischemic myocardium during angioplasty. It is surprising, however, that the increasingly popular partial cardiopulmonary bypass support for high-risk angioplasty is not discussed. The omission of an illustration of the business end of the angioplasty balloon catheter from chapter 1 must surely represent an oversight, as the other angiograms and illustrations are pertinent and of high quality.

In part II, application of coronary angioplasty to specific patient populations, such as those with multivessel coronary artery disease, and individuals who have unstable angina and acute myocardial infarction, or those who have had a previous coronary bypass operation, is thoroughly discussed. Although the results of the multiple trials of thrombolysis, with and without mechanical intervention, after acute myocardial infarction are described, one remains somewhat confused regarding the authors' recommendations, perhaps because the final trials were not yet reported.

The concept of the "culprit lesion" is again elaborated. However, I feel that such an approach often fosters excessive application of single vessel angioplasty in multivessel disease. The same cardiologists who in the past have been critical of surgeons performing incomplete revascularization and have urged more and more anastomoses to be done to smaller and smaller vessels of questionable significance are now quite comfortable with their ability somewhat subjectively to select that vessel most readily dilated. They also may not question the resulting incomplete revascularization, knowing they will probably get another opportunity to intervene in the future. A refreshing final chapter of this section is the discussion of laser application both to coronary and peripheral arteries. The widely described mechanical atherectomy catheter device is not included, however.

It is in part III, where complications and results of angioplasty are discussed, that the surgeon will probably have the most interest. Ponderous terms such as *spasmogenic mechanisms* and *thrombogenic melieu* may cool the reader's ardor for a review of complications, but he or she will undoubtedly become refocused on the subject by statements such as "subintimal coronary dissection represents a *minor* complication if the lumen is impinged upon by less than 50% or the pressure gradient is less than 20 mmHg." The major and minor complications of coronary angioplasty are well described, although I am not favorably impressed by the use of catheterization laboratory jargon with rather prurient overtones to describe such maneuvers as temporary wedging of the guiding catheter to provide support for the advancing dilating catheter. The authors have rightly pointed out, and it must be emphasized again, that the performance of emergency coronary artery bypass grafting after coronary angioplasty represents not a complication of percutaneous transluminal coronary angioplasty but rather an attempt to prevent or correct the complication.

In the discussion of the role of the surgeon, the provision of "formal standby" is the only mechanism of backup that is considered. A review of practices in other institutions where the patient may be taken to the "next available operating room," where stents and bail-out catheters may be relied on, or even where definitive surgery may be performed in a combination catheterization laboratory/operating room is not discussed. Furthermore, the ethical and legal obligations assumed by the standby surgeon and anesthesiologist, to say nothing of the incremental health care costs ascribable to the empty standby operating room, warrant discussion.

The eventual role of coronary angioplasty in the treatment of atherosclerotic heart disease remains unclear. The economics of repeated angioplasty versus a more definitive coronary bypass procedure done with long-lasting internal mammary artery conduits have been and will continue to be challenged. Similarly, maneuvers to reduce the restenosis rates such as insertion of stents have yet to be widely applied and withstand the scrutiny of time. This monograph, *Coronary Angioplasty*, edited by Dr Goldberg, is a useful and comprehensive document, compact and concise enough to be read cover to cover by surgeons and anesthesiologists dealing daily with patients undergoing this procedure as well as by other physicians wishing to know rather more than "what it's all about."

Burlington, Vermont

Dorsal Mass in Hyperparathyroidism Secondary to Chronic Renal Failure

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A 65-year-old man had metastatic calcification forming a huge mass located on the dorsum. The calcified mass extended into the thoracic cavity and was removed; the sixth rib was also resected. Diagnosis and treatment are discussed.

(Ann Thorac Surg 1989;48:426–7)

Metastatic calcification forming a periarticular mass sometimes occurs in patients with chronic renal failure. We report findings in a 65-year-old man with a huge mass on the dorsum as a consequence of metastatic calcification.

A 65-year-old Japanese man came to the Second Department of Surgery, Kyushu University Hospital, with the complaint of a mass on his back (Fig 1). He had been under hemodialysis elsewhere for chronic renal failure. He had received treatment three times weekly for 5 years. Aluminum hydroxide had been withdrawn for the last 9 months, since hyperaluminemia occurred. Physical examination revealed a nontender, partially hard and partially soft mass measuring 17 × 12 × 4.5 cm on the left dorsum. Serum calcium level was 12.3 mg/L; phosphorus level was 5.9 mg/L. Serum parathyroid hormone level was elevated to 5.4 ng/mL. Chest x-ray film showed calcification in the mass (Fig 2). Computed tomography (Fig 3) demonstrated a lobulated mass filled with high-density materials and forming fluid level. The tumor extended partly into the thoracic cavity. Bone scintiscanning (technetium 99m-labeled hydroxymethylene diphosphate, 20 mCi) revealed high-uptake spots around the left elbow, left shoulder,

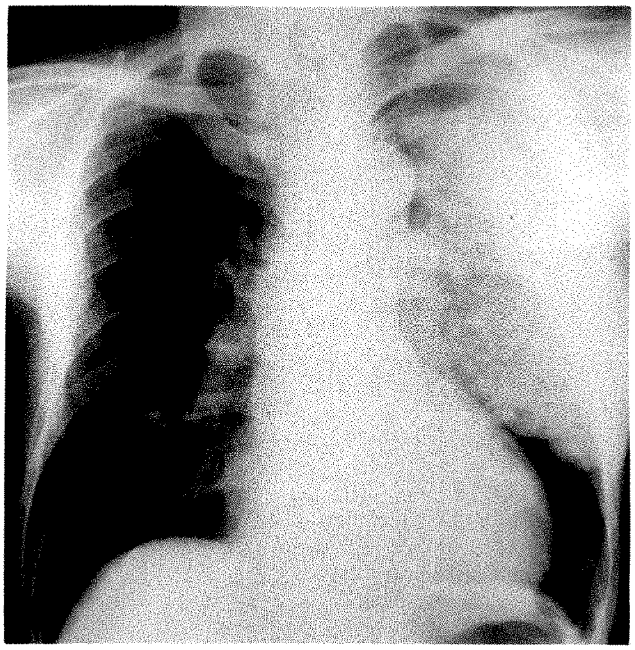

Fig 2. Chest x-ray film shows a calcified mass.

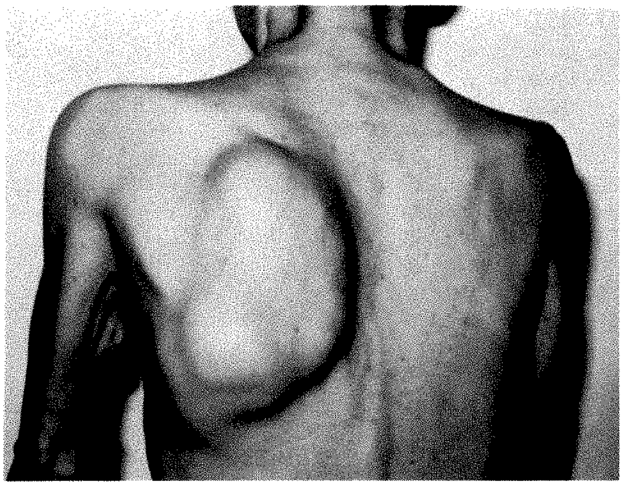

Fig 1. Huge mass on the dorsum of a 65-year-old man.

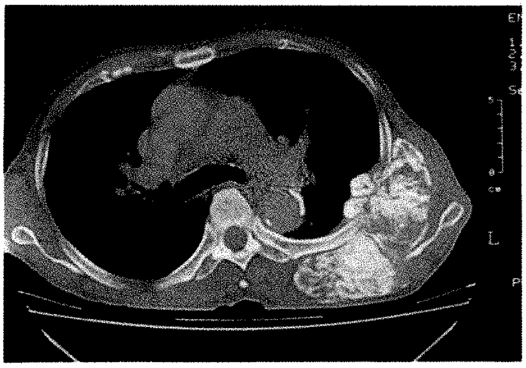

Fig 3. Computed tomographic scan of the chest shows extension into the thoracic cavity.

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and right hip joint, as well as on the left back (Fig 4); the calcified, lobulated mass was evident on the conventional x-ray film in each of these areas. Aspiration cytology from the back tumor produced a slightly yellowish-white, cloudy material. The patient requested surgical removal of the most disturbing huge lump on the back.

At operation, the mass and the sixth rib were excised. The tumor had grown expansively into the thoracic cavity and was covered with seemingly normal parietal pleura, but did not adhere to or invade the intrathoracic structure. The surgical specimen weighed 800 g. The cut surface revealed numerous cysts, each of which was filled with a yellowish-white pasty material (Fig 5). Recovery was uneventful, and hemodialysis is being continued three times weekly.

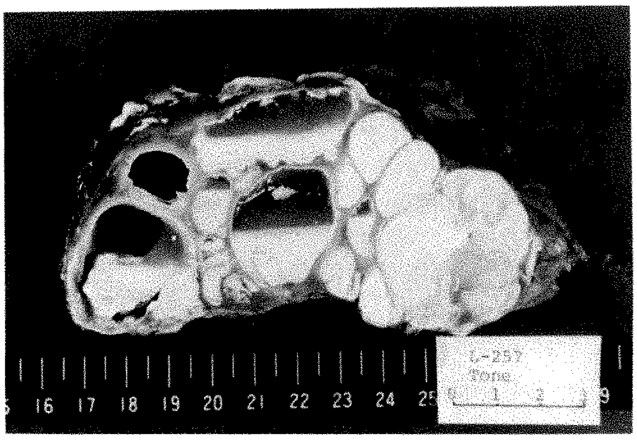

Fig 5. Cut surface of the tumor showing a multilobulated cystic mass filled with amorphous white material.

Comment

Secondary hyperparathyroidism associated with chronic renal failure often leads to calcification of soft tissues [1–4]. This metastatic calcification appears to occur when the plasma calcium and phosphorus product exceeds 70 [2, 3]. The calcified mass, mainly consisting of calcium phosphate [1, 5–7], usually occurs about the hips, elbows, and shoulders and resembles tumoral calcinosis. Tumoral calcinosis is a separate entity, although it also can manifest as a periarticular, multilobular calcified mass [5–7]. Tumoral calcinosis differs from metastatic calcification in chronic renal failure in that it occurs in otherwise healthy patients and the serum calcium and parathyroid hormone levels are within normal limits [5–7]. To our knowledge, a metastatic calcification occurring on the dorsum remote from any specific joint and extending into the thoracic cavity has never been reported. Thus, thoracic surgeons should be aware of this occurrence when making a differential diagnosis of chest wall tumor. Computed tomographic scanning, bone scintiscanning, and aspiration biopsy are diagnostic. Fluid level formation observed on conventional x-ray film is a prominent diagnostic characteristic [1], although it was not evident in the present case. We found that computed tomographic scanning more clearly visualized the internal structures of the tumor, including fluid level.

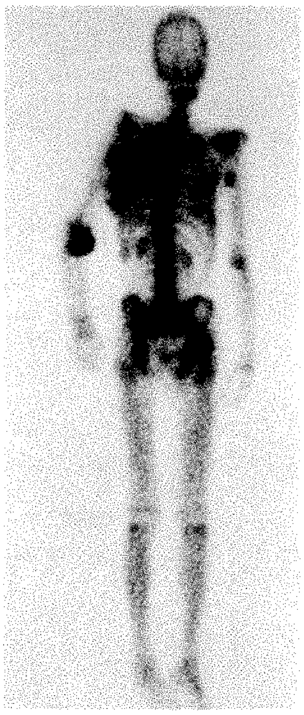

Fig 4. Bone scintiscan from anterior view. High-uptake areas are evident on the back, left elbow, left shoulder, and right hip joint. (Courtesy of Dr T. Tahara, Department of Radiology, Kyushu University Hospital.)

The treatment is symptomatic. Smith and Junor [1] reported that extended dialysis time and administration of aluminum hydroxide leads to removal of calcium deposits. However, surgical removal appears to be necessary if the tumor is large or becomes symptomatic. Total parathyroidectomy and autotransplantation may be indicated for select patients [8].

We thank M. Ohara for comments.

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Controversies in Management of Sternal Tumors

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The rarity of sternal tumors makes a good comparative study a difficult task. Controversies exist on questions of method of surgical diagnosis, the extent of the surgical procedure, and the different ways and means of reconstruction. We describe a case that was believed to be a clear case of chondrosarcoma but was actually a plasmacytoma. From the evidence of this case and a review of the literature we conclude that almost any plasmacytoma should be considered generalized multiple myeloma. Biopsy should be performed in all cases of sternal tumor before any surgical action is taken.

(Ann Thorac Surg 1989;48:428–31)

A 50-year-old man noticed a tender mass on his chest wall for one and a half weeks before admission. The patient denied any trauma or history of fever, chills, nausea or vomiting, difficulty in swallowing, or difficulty in breathing. Physical examination showed nothing remarkable except for an 8 × 8-cm mass, which was fleshy and fixed to the manubrium and sternum; the area was tender. No pulsation was noted. Admission laboratory data were within normal limits. A skeletal survey of the patient was negative except for the manubrium; bone scan was also negative.

A roentgenogram of the sternum and a computed tomographic scan showed a layered mass with bone destruction at the manubrium (Fig 1C). These findings were highly suggestive of a chondrosarcoma. Although most investigators today advocate biopsy before surgical planning, some still advocate surgical excision in such tumor cases [1, 2], especially when a case can be made for surgical excision of local plasmacytoma.

Technique

At operation, the manubrium of the medial two thirds of the clavicles as well as of the cartilage of the first and second ribs were widely excised to include the tumor and the involved skin. Figures 1A and 1C show the tumor before it was removed. Finger exploration behind the manubrium was performed to assure that the tumor did not invade mediastinal structures. The tumor was removed without breaking the pleuras. Figure 2B shows the chest defect after the tumor was removed. Both pleuras were intact.

Reconstruction

Because we removed the manubrium in its entirety and the clavicles partially, we chose a prosthetic material to reconstruct the parts and close the gap, both to obviate the need for long intubation and for protection of the mediastinal structures, as well as for cosmetic reasons. We used a methylmethacrylate sandwiched in a Prolene mesh, as shown in Figures 2C and 2D. Before cure, the mesh was applied in the gap for proper shape. To protect the tissues from the excessive heat produced by the curing of the methylmethacrylate, we applied a wet gauze to separate the mediastinal structures from the newly formed plate. We then removed the plate from the wet gauze and drilled quarter-inch holes (Fig 2D). We fixed the plate in place with interrupted wires to the clavicles, the ribs, and the remaining sternum (Figs 1D, 2D).

Muscular Reconstruction

We believed that freeing the skin down to the xyphoid and laterally to the nipples would allow a primary closure of the skin in a T shape (Fig 3). Both pectoralis muscles were separated from the distal insertion in the ribs and could easily be sutured together above the prosthetic plate (Fig 3). The humeral insertions of the muscles were left intact. A sump drain was inserted. The skin was closed as described (Fig 3D). Postoperatively, the patient did very well. After the wound had healed, he had a stable and hard sternum. Because the humeral insertions of the pectoralis muscles were not reseated, the patient had no functional deficits. Microscopic study has shown that the tumor is a plasmacytoma. Although a case can be made for resection of local myeloma, we believed that the prognosis was probably poor. This patient had no signs of a myeloma, yet a bone marrow biopsy showed that the patient indeed had generalized multiple myeloma. He was treated with melphalan and prednisone and was discharged from the hospital in good condition.

Comment

The methods of managing tumors of the sternum are still controversial. Investigators agree, however, that most sternal tumors are malignant and that all sternum tumors should be considered malignant until proved otherwise.

Most investigators now advocate a biopsy before oper-

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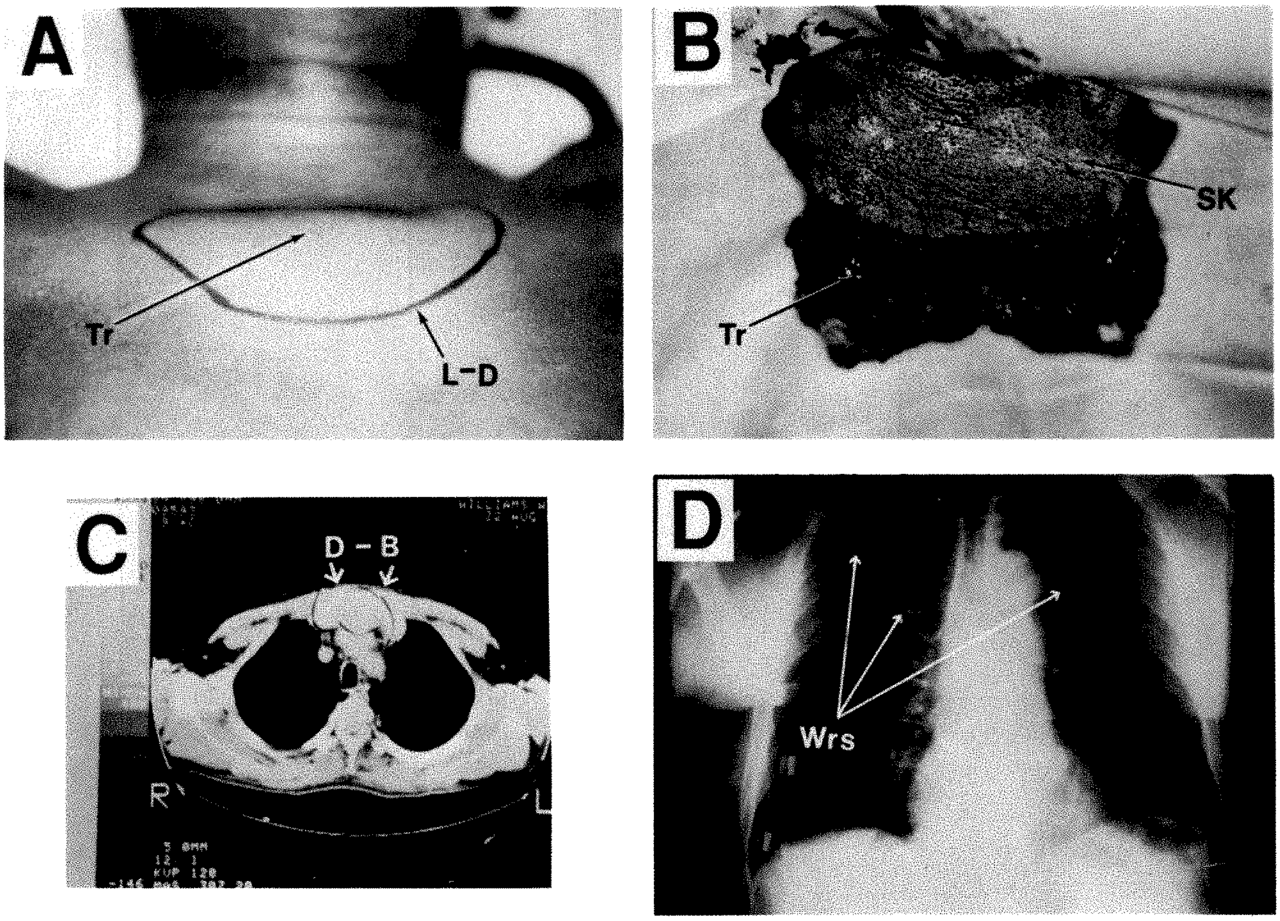

Fig 1. (A) Elevation of the skin. (B) Tumor (Tr) and skin (SK) removed, showing the size of the tumor and the skin removed. (C) Computed tomographic scan at the manubrial level, showing the destroyed sternum and calcification. (D) Chest roentgenogram postoperatively showing the wires (Wrs) holding the prosthesis. (D-B = destroyed bone; L-D = line of demarcation, ie, margin of skin to be removed.)

ation [3–5]. Our present case reinforces this attitude, as well as the claim that there is no such thing as "localized myeloma." It is always a metastatic disease. It can be a Ewing's tumor, in which case chemotherapy followed by operation gives better results than operation and radiotherapy. It can be Hodgkin's lymphoma or metastatic carcinoma.

As for surgical management, the wider the excision, the better. Whether total sternectomy must be performed remains an open question. Should we remove the tumor only? What should be the margin around the tumor? Should we remove the sternum in its entirety or partially, including the inner part of the ribs and the xyphoid? Most authors prefer partial resection [3–6], whereas others believe that total sternectomy must be performed because of the tendency for recurrence, especially in chondrosarcoma of the sternum [6]. Although resection of multiple recurrences has been reported with some success, we advise removing the sternum in its entirety to prevent recurrence because the disease can spread through the bone marrow to other parts of the body.

The reconstruction must include some means of preventing respiratory deficit, even for a short time. One-week endotracheal intubation may cause serious morbidity. Even if the patient does well, an unstable mediastinum can cause a long-term respiratory deficit. Protection of the mediastinal structures is also important. Use of methylmethacrylate in clean cases is recommended even if only for cosmetic reasons.

Describing the function of the sternum in the movement of the chest cavity may be useful (Fig 4). Present a summary of the functional loss according to the part of the sternum removed [7, 8]. The pectoralis muscles can be used to cover the sternal area without separation of the humeral insertions.

Reconstruction for sternal osteomyelitis is more successful [9] without prosthetic material probably because the mediastinum is already stiff due to the previous open heart procedure, and prosthetic material tends to become infected. Thus, we do not recommend its use. As for skin reconstruction, we strongly recommend making an effort to use the surrounding skin to cover the defect formed by removal of the tumor as we have done. With this primary closure, there is no risk that a skin graft will not "take." It is also cosmetically more appealing than the myocutaneous flap.

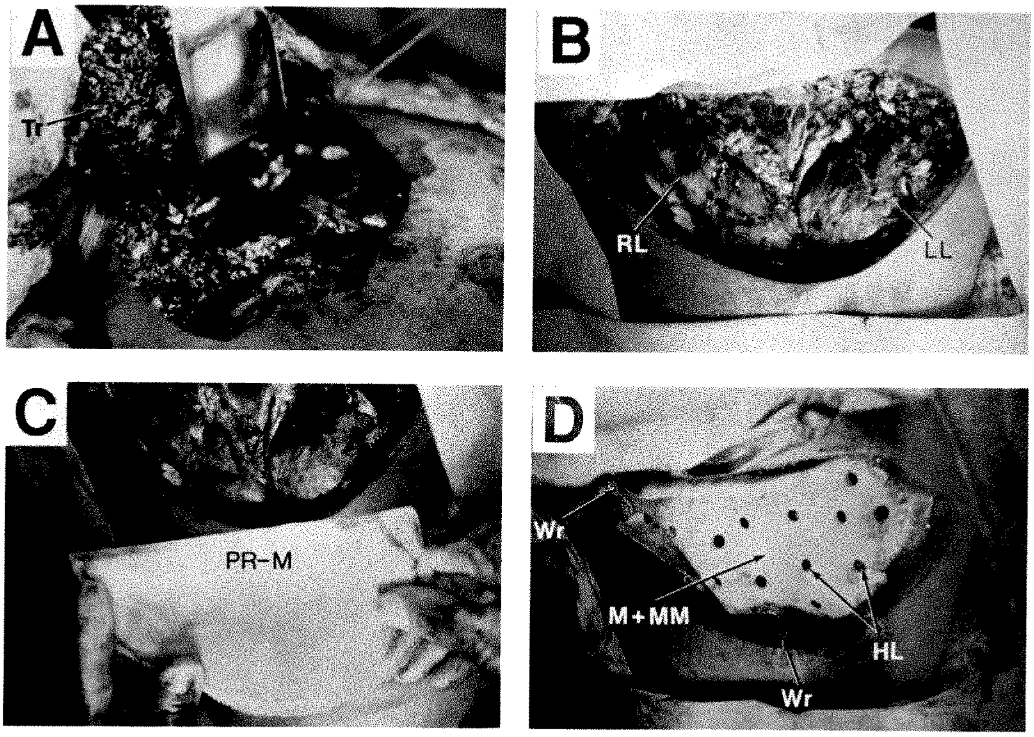

Fig 2. Prosthetic reconstruction. (A) Both medial clavicular heads were resected. The tumor (Tr) *was resected from the sternal side and was ready to be removed en bloc. (B) Remaining defect after tumor was removed. Upper right lung* (RL) *and left lung* (LL) *can be seen. Neither pleura was penetrated. (C) Folded Prolene mesh* (PR-M) *fitted to the size of the defect. (D) Prolene mesh and methylmethacrylate "sandwich"* (M&MM) *were fixed to the clavicles, the ribs, and the upper part of the remaining sternum with wires* (Wr). *Multiple holes* (HL) *were drilled before insertion.*

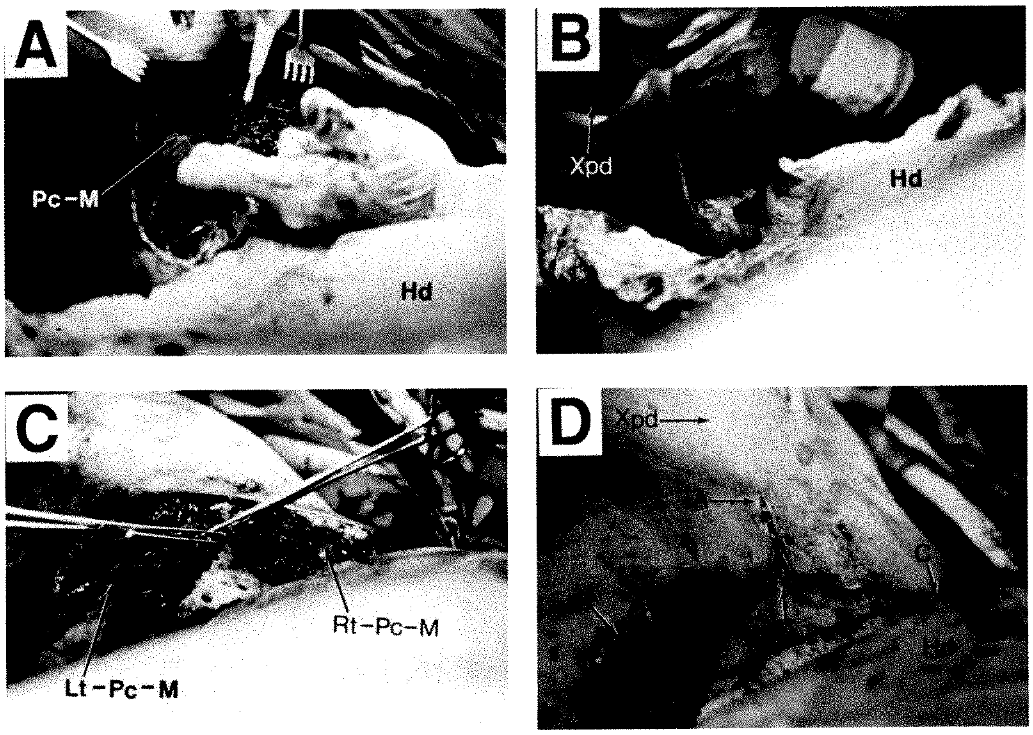

Fig 3. Muscular and cutaneous reconstruction. (A) The distal part of both pectoralis muscles (Pc-M) *was separated from the rib cage. (B) The skin was separated from the rib cage down to the xyphoid* (Xpd) *and laterally beyond the nipples. (C) Approximation in midline of both pectoralis muscles. The prosthetic material underneath is apparent. (D) The skin was approximated in a T fashion. The skin at points* A, B, *and* C *had created an elevation that had to be removed and flattened.* (D = *the point of contact between the two lateral parts and the upper portion of the wound;* Hd = *head of the patient;* Lt-Pc-M = *left pectoralis;* Rt-Pc-M = *right pectoralis.)*

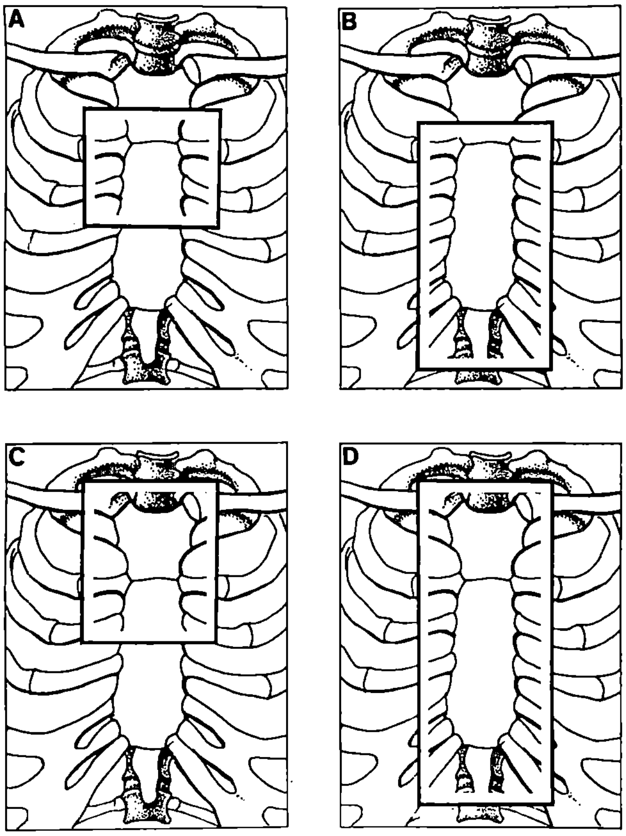

Fig 4. (A) Loss of upper sternal body and adjacent ribs. Physiological deficit is not clinically significant. (B) Loss of entire sternal body and adjacent ribs. Moderate physiological deficit, correctable by reconstructive operation; ventilation by tracheostomy is required for a short time. (C) Loss of manubrium and upper sternal body with adjacent ribs, manubrium, clavicles, first through fifth cartilage, and ribs. Diaphragmatic components are not impaired, but severe deficit exists. Reconstruction is necessary, and tracheostomy is needed for several weeks unless hard prosthetic material is used. (D) Loss of the total sternum including the manubrium and the medial parts of the clavicles causes severe respiratory deficits because the diaphragmatic components are also impaired. Reconstruction is necessary, including use of hard prosthetic material if prolonged intubation and postintubation complications are to be avoided.

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Ductus Diverticulum Aneurysm and Coronary Stenosis: Repair Using Circulatory Arrest

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The case of a 68-year-old man with advanced symptomatic coronary artery disease and large aneurysm of the diverticulum of the ductus arteriosus is presented. Both the coronary artery disease and the aneurysm were successfully repaired at the same time via median sternotomy using cardiopulmonary bypass and a brief period of profound hypothermic circulatory arrest. To our knowledge, this is the 27th reported case of such an aneurysm in an adult.

(Ann Thorac Surg 1989;48:432–3)

A 68-year-old man was seen in the clinic for a history of progressive dyspnea on exertion and frequent episodes of chest pain. A chest roentgenogram showed a mass in the region of the left main pulmonary artery. He was admitted for further evaluation.

A complete blood count, automated chemistries, urinalysis, and resting electrocardiogram were normal. Pulmonary function tests showed a moderate restrictive defect. A ventilation-perfusion scan was normal. Computerized axial tomographic scan with contrast of the chest was interpreted as demonstrating an aneurysm of the left main pulmonary artery; however, a pulmonary arteriogram was normal.

Cardiac catheterization showed normal saturations and right-sided pressures, severe three-vessel coronary artery disease, and near-normal left ventricular function. An aortogram showed a 6.5-cm saccular aneurysm arising from the junction of the transverse and descending thoracic aorta and extending anteromedially (Fig 1).

The aneurysm, easily accessible through a median sternotomy, was located between the aortic arch and left pulmonary artery. Thrombus and aneurysmal debris were seen extruding through a 2-cm erosion of the left superior pericardial reflection. Left femoral artery and two-stage right atrial cannulas were used to institute cardiopulmonary bypass at 2.4 L/min/m^2 at 25°C. Intermittent cold sanguineous cardioplegia, topical ice slush, and a transmitral left ventricular vent were used for myocardial protection. The aorta was cross-clamped while four distal coronary anastomoses were performed. The cross-clamp was removed (42 minutes), and the patient was further cooled to a nasopharyngeal temperature of 20°C while the great vessels were individually exposed. A single vascular clamp was then applied to the upper cuff of the transverse arch, occluding the origin of the great vessels. Total circulatory arrest was initiated. The aneurysm was opened longitudinally, and thrombus was evacuated. A 4 × 2.5-cm defect in the aorta, composed of firm fibrous edges with no "neck," was closed with a preclotted double-velour woven Dacron patch. After a circulatory arrest period of 18 minutes, the aortic arch was vented, the patient was placed in the head-down position, and femoral artery flow was started slowly. Air removal maneuvers were undertaken, and the great vessel clamp was removed. The heart regained spontaneous normal sinus rhythm during rewarming and construction of the proximal saphenous vein anastomoses. The patient was easily separated from cardiopulmonary bypass using an infusion of dopamine (5 μg/kg/min).

The next day, the patient was weaned from catecholamine support and was neurologically normal. He was extubated after diuresis of retained fluid. Copious secretions and left lower lobe collapse later necessitated reintubation and ventilation for an additional two days before successful extubation. The remainder of his recovery was uneventful.

Comment

Aneurysms of the diverticulum of the ductus arteriosus are rare in adults. The literature contains 26 reports of such aneurysms [1–5], 21 of which are found in a recent review [1]. More than half are associated with death from erosion into a bronchus, the esophagus, pulmonary artery, or pericardium. Although we found no communication with the pulmonary artery or remnant of ligamentum arteriosum in our patient, the location, size, shape, rim of fibrous tissue at its opening, and lack of atherosclerotic changes in the surrounding aorta support the diagnosis of aneurysm of the ductus diverticulum [2].

Recently, the Stanford group reported successful repair in 5 patients [1]. Two aneurysms were repaired through a left posterolateral thoracotomy using partial cardiopulmonary bypass, and three were approached through a median sternotomy. In 1 patient who had associated coronary artery disease, revascularization was performed initially, followed by an aneurysmorrhaphy during rewarming using a partial occlusion clamp.

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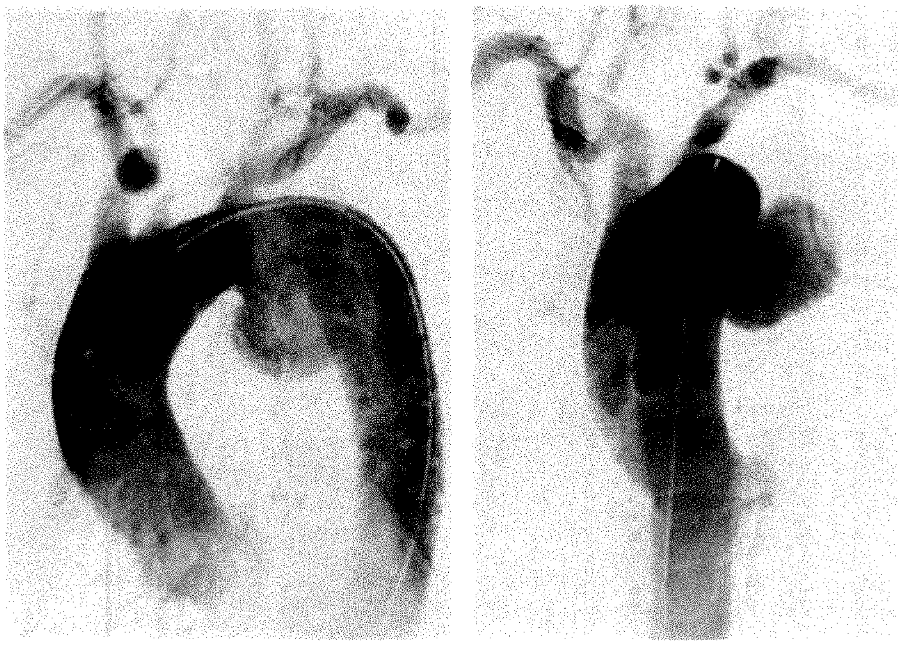

Fig 1. Anteroposterior and lateral subtraction aortogram showing aneurysm of the diverticulum of the ductus arteriosus.

Our patient's severe coronary artery disease and unstable symptoms dictated that revascularization either precede or be performed concomitant with aneurysm repair. The size of the aneurysm and its impending rupture precluded safe placement of a partial occlusion clamp as well as any consideration of staged repair. Bypass grafting and concomitant aneurysm repair using circulatory arrest appeared to be the best choice.

Not only can these aneurysms rupture during the natural course of disease, but, because of their size and location, they can also result in compromise of the phrenic or recurrent laryngeal nerves. It is of interest that 4 of the 5 patients reported by the Stanford group initially had hoarseness. Our patient's recurrent laryngeal nerve was normal preoperatively and was somehow spared during operation. However, his left phrenic nerve was damaged either during revascularization or, more likely, during aneurysm repair and was contributory to his left lower lobe collapse and to the difficulty in weaning him from the ventilator. Attempt should be made to avoid damage to these nerves during aneurysm repair when possible.

Coronary revascularization and repair of the aneurysm of the ductus diverticulum using median sternotomy and a brief period of hypothermic circulatory arrest proved to be a safe and effective alternative, providing optimal exposure. Because no mobilization of the aorta near the aneurysm was necessary, the risk of premature rupture or injury from the clamp was avoided.

We thank Sue Lowe for secretarial assistance in the preparation of the manuscript.

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Combined Revascularization of Coronary and Femoral Arteries: A Proposed Alternative

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Two patients with both coronary artery disease and leg ischemia were successfully treated with a combined revascularization procedure. Coronary arteries were bypassed with in situ internal mammary artery grafts, and bilateral femoral arteries were bypassed with expanded polytetrafluoroethylene grafts descended from the ascending aorta through the preperitoneal abdominal wall tunnel. Both patients recovered well and experienced no angina or claudication.

(Ann Thorac Surg 1989;48:434–6)

Coexistent occlusive disease in the coronary and the aortoiliac arteries has been noted in relatively high incidence [1, 2]. To bypass both coronary and femoral arteries simultaneously, a new combined procedure was attempted in 2 patients. All stenosed coronary arteries were bypassed with in situ internal mammary artery (IMA) grafts, and bilateral femoral arteries were bypassed with expanded polytetrafluoroethylene (PTFE) grafts descended from the ascending aorta through the preperitoneal abdominal wall tunnel. Both patients recovered well and experienced no angina pectoris or claudication.

Patient 1

A 65-year-old man suffered from severe intermittent claudication after walking 50 m for 2 years. Because of recent onset of chest pain, angiography of the coronary artery and the aorta was performed. It showed left main coronary artery stenosis and complete obstruction of the abdominal aorta just below the renal arteries. Both femoral arteries were perfused through multiple small collateral vessels. Simultaneous revascularization of coronary and femoral arteries was performed in January 1988 using bilateral in situ IMA and PTFE grafts. The left anterior descending artery was bypassed with the right IMA, and the first diagonal branch and the obtuse marginal branch were bypassed with the left IMA sequentially. All these anastomoses were performed with a continuous suture technique with single 8-0 Prolene. After declamping the aorta, a PTFE graft (Impra Flex 7 mm) was anastomosed to the ascending aorta under the side bite clamp using 5-0 Gore-tex suture. Then a PTFE graft was passed through the preperitoneal abdominal tunnel and through the rectus muscle at the groin, and anastomosed to the right femoral artery. The left femoral artery also was bypassed with the PTFE graft in modified femorofemoral bypass fashion as shown in Figure 1. The patient recovered uneventfully, and angina and claudication completely disappeared. Postoperative angiogram revealed patent IMA and PTFE grafts.

Patient 2

A 65-year-old man suffered from angina pectoris for 15 years and claudication after walking 100 m for 7 years. He

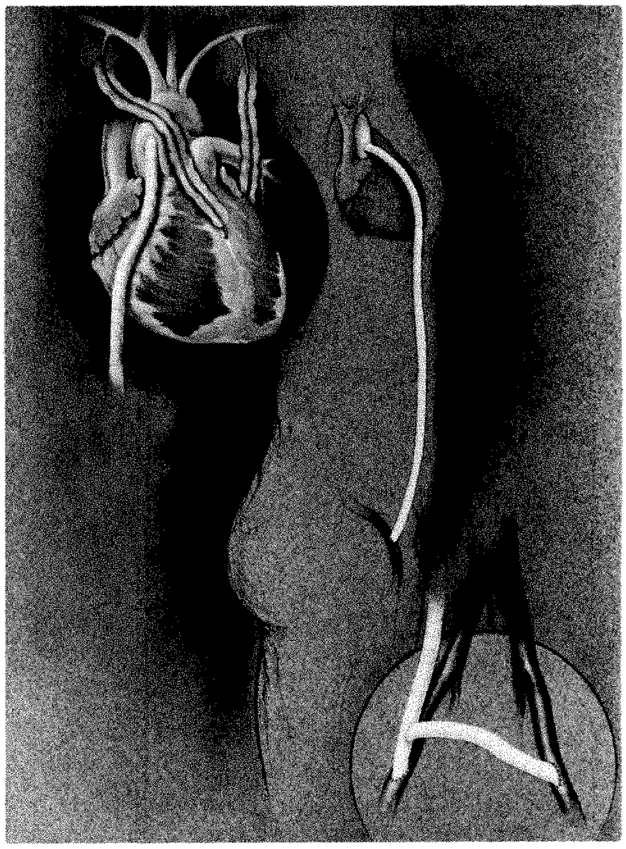

Fig 1. Scheme of the procedure. Coronary arteries were bypassed with in situ internal mammary artery grafts, and femoral arteries were bypassed with expanded polytetrafluoroethylene grafts descended from the ascending aorta and passed through the preperitoneal abdominal wall tunnel.

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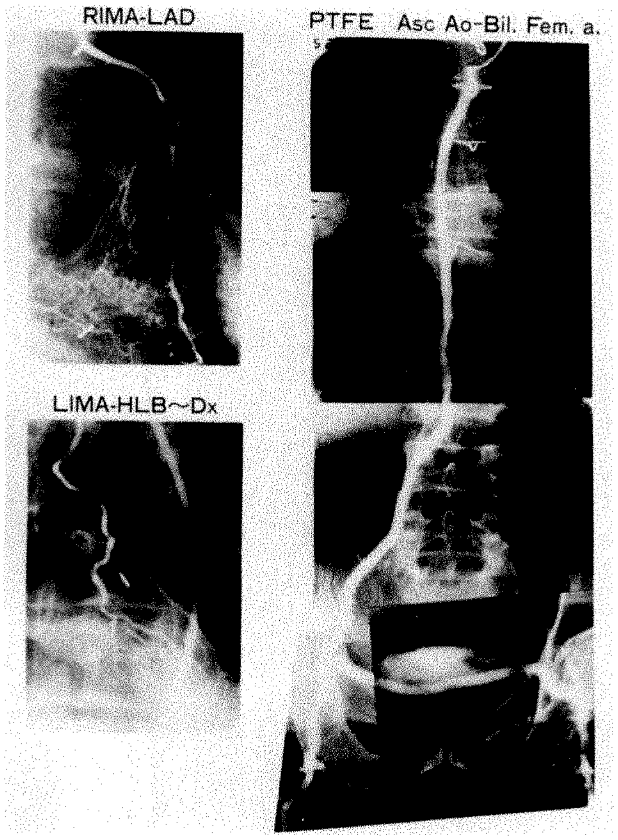

Fig 2. Postoperative angiogram of patient 2. The left anterior descending artery (LAD) *was bypassed with the right internal mammary artery* (RIMA) *(left, top) and the diagonal* (Dx) *and the high lateral branch* (HLB) *were bypassed with the left internal mammary artery* (LIMA) *sequentially (left, bottom). Bilateral femoral arteries* (Bil. Fem. a.) *were bypassed with polytetrafluoroethylene* (PTFE) *grafts from the ascending aorta* (Asc Ao) *(right). All grafts were patent.*

also suffered from diabetes mellitus and required insulin. Angiogram showed severe triple coronary artery stenoses, complete obstruction of the left iliac artery, and severe stenosis of the right iliac artery. Electrocardiogram showed deep Q wave in leads II, III, and aVF. Operation was performed in April 1988 using the same procedure as in patient 1. Patient 2 also recovered well and experienced no angina or claudication. All grafts were patent at 2 months after operation (Fig 2).

Comment

Combined cardiac and aortoiliac artery operation recently has been performed with an acceptably low risk [3]. Simultaneous revascularization of both coronary and femoral arteries is advantageous in terms of a shorter duration of hospital stay and a faster progress of postoperative rehabilitation for patients with angina and leg ischemia. However, the ordinary femoral artery bypass procedure requires an additional incision to expose the subclavian artery for axillofemoral bypass or intraabdominal manipulation for direct aortoiliac-femoral bypass. Baird and associates [4] described their 10 years' experience with extraperitoneal ascending aorta to bifemoral bypass with 18 patients including 3 who required coronary artery bypass grafting simultaneously. The 5-year patency rate of this particular graft was 70%. As they mentioned, the graft positioned behind the rectus muscle is not visible, palpable, or compressible. Although this procedure may be limited only to patients unable to undergo standard intraabdominal repair if their symptom is leg ischemia only, it is more justified when the patient requires revascularization of both coronary and femoral arteries because sternotomy is essential. In our method using in situ IMA grafts for coronary artery revascularization, the ascending aorta can be completely free from vein graft anastomoses, so that the anastomosis of a PTFE graft to the aorta is much easier. A PTFE graft can be easily led to the groin through the abdominal wall tunnel without laparotomy, and spiral beading is protective against kinking of the PTFE graft. We believe that this procedure is preferable for patients with coronary artery disease and leg ischemia both in terms of favorable long-term results of the coronary artery bypass graft due to excellent patency of the IMA [5] and in terms of the technical simplicity of femoral artery bypass with the PTFE graft anastomosed to the ascending aorta without any additional incision.

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INVITED COMMENTARY

It has been 12 years since I described the use of the ascending aorta as a source of inflow for a graft to the femoral arteries (Ann Surg 1977;186:210-2). The operation was devised for patients with severe leg ischemia who were not suitable for standard aortofemoral bypass. The most common indication was an unapproachable abdomen and previous failure of the standard operation. With a past history of graft failure in so many patients, I was gratified that the 5-year patency of 70% was only slightly less than that achieved with the standard operation, and considerably better than the long-term patency achieved with axillofemoral bypass. With our stringent selection criteria, the operation has been performed on only 2 to 3 patients a year, and my total series is now 28 patients.

As Suma and co-workers point out, the operation is technically easy for anyone trained in both vascular and cardiac surgery. Such surgeons are now an aging generation in North America. Many of the younger vascular surgeons are not comfortable with a sternotomy or the ascending aorta; I believe this explains the low number of cases reported on this continent. It is easy to perform a concomitant cardiac procedure, and we have done so in 5 patients. The tunneller does not need to go "through the rectus muscle at the groin," but runs in the space in front of the posterior rectus fascia to the arcuate line, and then in the preperitoneal space to the groin. Here it appears in much the same fashion as the standard graft coming from the retroperitoneal space. It is appropriate to attach the distal end to the arc of a crossfemoral bypass graft.

The second patient reported by Suma and co-workers, with iliac occlusion on one side and iliac stenosis on the other, might have been more appropriately treated by percutaneous transluminal dilation of the stenosed artery, followed by a standard cross-femoral bypass graft.

I congratulate Suma and co-workers on bringing this operation to the attention of thoracic surgeons.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. They should also keep a record of their attendance at thoracic surgical meetings, and other continuing medical education activities, for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS III syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS III booklets prior to applying for recertification. SESATS III booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1992 may begin the recertification process in 1990. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is July 1, 1990. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Mitral Annular Calcification: A New Technique for Valve Replacement

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Many dangers attend mitral valve replacement in the presence of dense posterior annular calcification. The procedure described has been successful in 4 patients. The major elements of this procedure include complete ultrasonic debridement of the calcification, reconstitution of the disassembled atrioventricular groove, and retention of the mitral valve leaflets.

(Ann Thorac Surg 1989;48:437–9)

Mitral annular calcification may cause mitral regurgitation and stenosis. The calcified annular bar poses demanding technical problems for the surgeon attempting mitral valve replacement. The mass of calcium interferes with suture placement and may restrict prosthetic valvular motion, and its debridement may lead to left ventricular rupture [1–5].

Techniques for valve replacement in the presence of annular calcification include anchoring the prosthesis to the mitral leaflets and avoiding the calcification [5], passing the sutures through or around the annular calcification [1], suturing the prosthesis above the annulus to the left atrial wall, and drilling through the annular calcium to create holes for the sutures [6]. Nevertheless, the operation still has considerable mortality (27% in-hospital and an additional 18% at 1 year) [1].

A different valve replacement technique used in 4 patients with severe mitral annular calcification achieved a good intraoperative result and an excellent postoperative course. The patients were similar: All were elderly women (aged 63, 67, 68, and 80 years) with severe mitral regurgitation. Two had concomitant coronary artery disease, a third had severe tricuspid regurgitation, and the fourth had no other cardiac disease. All had posterior mitral annular calcification extending in arcs of 180 to 270 degrees around the circumference. All 4 patients had mitral valve replacement, combined with coronary revascularization in 2 and tricuspid annuloplasty in 1. The fourth patient had no additional operative procedures. A St. Jude valve was used in each case.

During short-term follow-up of 1, 6, 9, and 10 months, respectively, no patient has had any clinical evidence of mitral regurgitation, ventricular rupture, or false aneurysm, and all are in New York Heart Association class I. One patient has a systolic murmur; 3 have no murmurs. Echocardiography demonstrates mild mitral regurgitation commensurate with that observed with St. Jude valves.

Technique

The calcification involved the annulus and the posterior leaflet in places, and extended down into the posterior left ventricular muscle. The following technique, applied in these 4 patients, permits extirpation of the calcified bar and mitral valve replacement.

After entering the left atrium through a standard incision posterior to the interatrial groove, make a circumannular incision in the left atrium a few millimeters peripheral to the calcification (Fig 1). This incision is very similar to that described by Cox and colleagues [7] for the approach to left free wall tracts in Wolff-Parkinson-White syndrome. Carry the incision through the atrial wall exposing the atrioventricular (A-V) groove fat pad (containing the circumflex coronary artery and great coronary vein) (Fig 1). The calcification lies immediately anterior and will be seen to extend into the annulus, into the A-V groove fat pad, sometimes into the valve leaflet, and into the posterior left ventricular wall. It is important to realize that the junction between the left atrium and mitral annulus and between the mitral annulus and left ventricle has already been disrupted, yet remains bonded together by the mass of calcium. With an ultrasonic debridement tool (Cavitron Ultrasonic Surgical Aspirator, Cooper, Stamford, CT), remove all the calcification (Fig 2). This requires removing calcium extending into the valve leaflet, the wall of the left ventricle, and the A-V groove fat pad. Total removal of the calcium insures that the remaining pliable tissue will easily coapt with and conform to the rigid prosthetic annulus. Use of ultrasonic debridement allows safe removal of the calcification and prevents the tearing of the A-V groove vessels that could occur from avulsion of the calcium. At the completion of the debridement, the cephalad aspect and both the external and internal surfaces of the left ventricular wall will be seen, now totally disconnected from the annulus where the calcium had been (Fig 3). If the calcification extends into and comprises the full thickness of the posterior mitral leaflet, the debridement necessarily removes the most peripheral portion of the leaflet. The more central portion of the leaflet remains attached to the chordae and papillary muscles but detached from the annulus.

Reconstruct the heart with the valve sutures. Teflon felt pledget-reinforced sutures may be passed through the atrial wall, cephalad to the A-V groove fat pad, through the cephalad aspect of the exposed left ventricular wall, around the remaining mitral leaflet, and then up through

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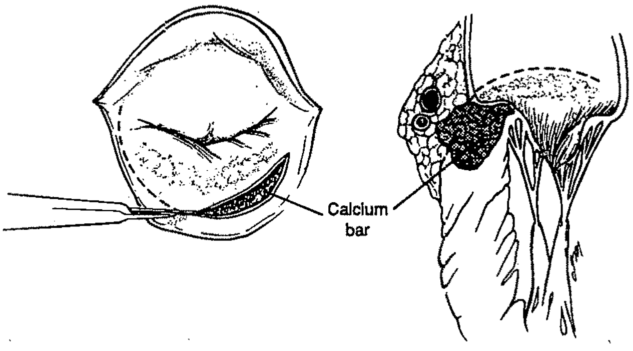

Fig 1. Incision is made through the left atrial wall, posterior to the mitral annulus and over the annular calcification.

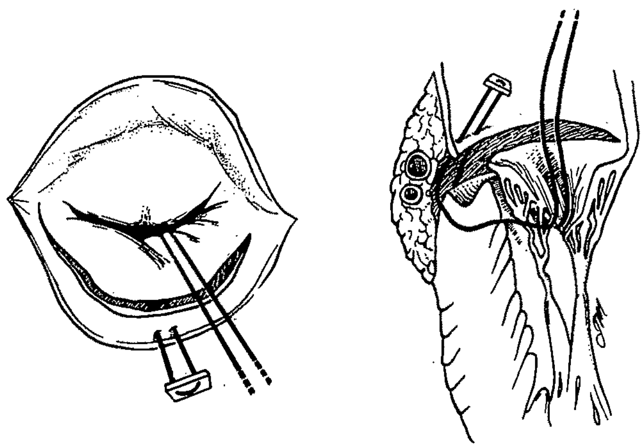

Fig 3. The annular region is reconstructed with the valve sutures. The sutures are buttressed with Teflon felt pledgets and inserted as horizontal mattress sutures passing through the atrial wall, then through the full thickness of the ventricular wall and, finally, around the retained mitral valve.

the sewing ring of the prosthetic valve (Figs 3–5). This achieves reconstitution of the heart, retention of the subvalvular apparatus, and reefing of the mitral leaflet to prevent its interference with the St. Jude valve leaflets. Place the anterior sutures through the periphery of the anterior leaflet and then around the leaflet to accomplish the same effect as with the posterior leaflet. It may be necessary to reduce the bulk of the anterior leaflet by excising from it a crescent that still preserves its connection to the primary chordae.

Comment

This valve replacement procedure avoids the disadvantages of techniques that do not remove the calcification. If the prosthetic valve is sutured to the left atrial wall, the bar of calcification below the prosthesis prevents use of a disc valve and may even prevent proper placement of a porcine valve, depending on the bulk of the calcification. If the prosthetic valve is sutured to the posterior mitral leaflet central to the calcified bar, use of a valve that is smaller than desired may be necessary. In addition, if the calcification extends into the valve leaflet, coaptation of the leaflet to the sewing ring may be compromised or the technique may be impossible. Complete debridement of the calcification prevents the problems that occur with each of these two techniques.

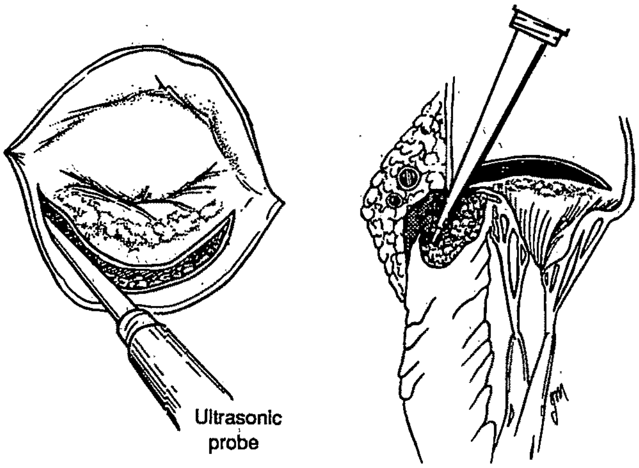

Fig 2. The calcification is completely debrided with the ultrasonic probe, resulting in disconnection of the left atrium from the left ventricle from the mitral valve; debridement of the calcification necessarily removes the annulus.

Because the bar of calcification separates the left ventricle from the mitral annulus, passing sutures around or through the bar, or partial debridement of the calcified bar without accurate reconstruction of the periannular anatomy, increases the risk of left ventricular or A-V groove rupture. This catastrophic event has been described by Dark and Bain [4], Roberts and Morrow [3], Spencer and associates [2], and Cammack and co-workers [1]. The technique we described in effect anticipates such a rupture by deliberately creating it intraoperatively and then carefully reconstituting the three structures confluent at the A-V groove. Because the prosthetic valve abuts against pliable tissues rather than against the rigid calcified bar, the risk of postoperative paravalvular leak should be reduced. Furthermore, blindly passing sutures around or through the calcified bar jeopardizes the circumflex coronary artery. Our technique allows the A-V groove fat pad and its contained vessels to fall posteriorly

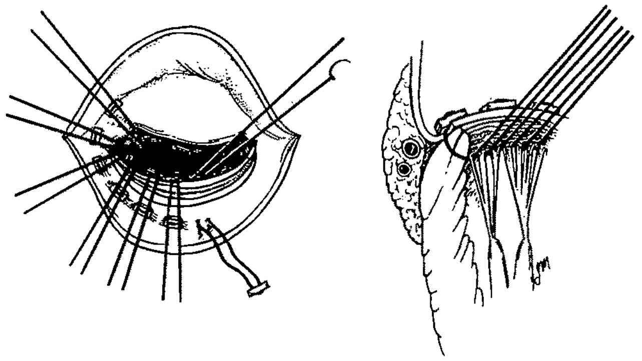

Fig 4. The sutures coapt the posterior left atrial wall, left ventricular wall, and posterior leaflet of mitral valve, thus reconstructing the annular region.

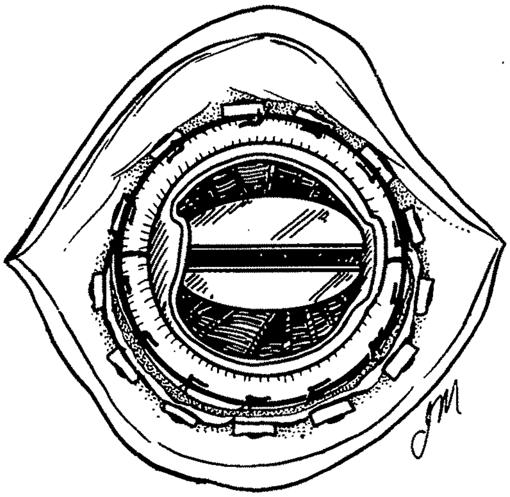

Fig 5. The sutures are passed through the prosthetic annulus, and the valve is tied into place.

and lie free of harm from sutures passed under direct vision.

Although this procedure has been designed to avoid the ventricular rupture that may accompany partial debridement of, or passage of sutures through, the calcium, risk of such rupture still exists with this procedure and constitutes a possible disadvantage. It is disconcerting to have disconnected left atrium from annulus from left ventricle. If the sutures cut through the left ventricular muscle, rupture will occur. No bleeding occurred in any of our patients, however, and the repair appeared to be secure as it was performed.

Retention of the mitral leaflets and the subvalvular mechanism reduces or eliminates the deterioration in left ventricular function that occurs after mitral valve excision [8–10]. Our procedure achieves that goal.

Eguaras and colleagues [11] recently reported use of ultrasonic debridement of aortic and mitral valves in explanted specimens but did not extend the technique to clinical use. Ultrasonic debridement of the bar calcification can also be used in conjunction with mitral valvuloplasty if the valve leaflet has not been destroyed by calcification. In all 4 of our patients, the calcification extended into the posterior mitral leaflets and constituted the entire thickness of the leaflets. Debridement of the calcification necessarily left insufficient valve leaflet for reconstruction. With mitral bar calcification alone and intact leaflets, however, reconstruction and retention of the native valve could be accomplished.

This valve replacement technique allows insertion of a full-sized mitral prosthesis, eliminates the problems associated with retention of the calcified bar in the mitral annulus, and permits retention of the mitral apparatus, which in turn provides better left ventricular performance. In this limited series of 4 patients, the short-term results have been excellent. We recommend continued evaluation of this technique when dealing with the vexing and dangerous problem of mitral annular calcification.

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A Method of Retraction During Reoperative Coronary Operations Using the Favaloro Retractor

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A method is described for using the Favaloro retractor to provide retraction during dissection of the anterior wall of the heart during reoperative cardiac operations.

(Ann Thorac Surg 1989;48:440)

Reoperative coronary artery bypass grafting is becoming increasingly common. In our practice, approximately 10% of our open heart procedures are reoperations. Also, it has become clear that the internal mammary artery is the conduit of choice whenever it is available [1, 2]. Frequently, the internal mammary arteries have not been used at the first operation and are still available at reoperation. In using the Favoloro retractor to dissect down the left internal mammary artery, we noted that it also made dissection of the anterior surface of the heart, particularly the areas overlying the ventricles, much easier, with much less strain on the operator and assistant.

We have used this method of retraction for more than 1 year. We like it so much that we have started using it for reoperations even when the left internal mammary artery is not being used.

Technique

The initial median sternotomy incision is made, and the sternum is cut with the oscillating saw. The underside of the sternum is freed enough to allow placement of the Favoloro retractor. The left side of the sternum is then retracted, and the plane of dissection is carried along the anterior surface of the right and left ventricle, with the retractor providing excellent exposure by placing steady tension on the adhesions over the anterior surface of the heart and providing easy access all the way to the apex. After the anterior surface of the left heart is freed, the Favoloro retractor is left in place and the left internal mammary artery is dissected down in the usual fashion using cautery and clips.

We find it easier to dissect out the heart first, because once the mammary pedicle is dissected down, the pedicle and the edge of the pericardium fall into the operator's field of view and make dissection of the adhesions over the heart more difficult.

After the left internal mammary artery is taken down, the aorta and the right heart are freed and the patient is cannulated for bypass in the routine fashion. We usually dissect out the posterior aspect of the heart after the start of bypass.

Comment

We describe a simple method for using the Favoloro retractor to provide exposure in dissecting out the anterior surface of the heart in reoperative cardiac operations. The Favoloro retractor provides strong and steady retraction and frees an assistant from a tedious task.

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Potassium-Induced Cardioplegia: Evolution and Present Status

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Most cardiac surgical procedures performed in 1989 are accomplished with the aid of some type of controlled, chemically induced cardiac standstill. Although the physiological principles involved were described in the late 19th century, the first clinical application was not until 1955. Because many surgeons believed that myocardial injury resulted from the toxicity of the agents used, the technique was largely abandoned for about 15 years. With the increasing volume of coronary revascularization surgery and with the need for protection of donor hearts intended for orthotopic transplantation, chemically induced cardiac standstill became more appealing and the technique was revived and reevaluated in several centers. In the last several years, the constitution of cardioplegic solutions and the methods by which they are delivered have been greatly modified. Although the most effective solution and technique may yet remain to be described, unquestionably controlled chemically induced cardiac standstill has contributed substantially to the ease and safety with which cardiac surgical procedures can be accomplished. This vignette, although far from complete, outlines some of the important works that have contributed to the evolution of cardioplegic techniques.

(Ann Thorac Surg 1989;48:441–3)

Observation that cations in the extracellular medium had a profound effect on cardiac action was first established by the classic studies by Ringer [1], which were published in 1883. After observing the disordered contractile pattern of ventricular fibrillation in experimental animals, Hooker [2] in 1929 suggested that a solution of potassium chloride might be used to alter this condition. In 1955, Melrose and associates [3] described both animal and clinical studies using a solution of concentrated potassium citrate to effect elective cardiac arrest and also described resumption of normal cardiac activity after reperfusion. In the same year, Lam and colleagues [4] in Detroit used high concentrations of potassium chloride for the same purposes with similar results. In 1959, Sealy and colleagues in Durham [5] used a solution containing potassium, magnesium, procaine, and neostigmine in a series of clinical cases. Use of induced cardiac arrest, however, fell into disfavor several years later after a report of some unexpected postoperative deaths that were seemingly related to administration of potassium citrate and after the description by Helmsworth and associates [6] of focal areas of microscopic myocardial injury believed to result from administration of a toxic substance. In 1960, Swedish investigators Bjork and Fors [7] reported that less myocardial damage resulted after a period of ischemia alone than when the ischemia was accompanied by either potassium- or acetylcholine-induced arrest.

The occurrence of unexpected deaths and the association of these deaths with chemically induced cardiac arrest resulted in virtual abandonment of the technique for nearly 15 years. During this time, cardiac operations were performed on the beating perfused heart, the intermittently perfused heart, or the ischemic topically cooled heart. Each of these techniques, although effective in some situations, leaves something to be desired both as a method of myocardial protection and as a technique for establishing a quiet and bloodless operative field.

After the studies of Wiggers [8] in 1954 examining the relationship between cardiac contraction and coronary blood flow, Sabiston and Gregg [9] in 1957 reported that the net effect of cardiac contraction was to impede coronary blood flow. In 1958, Beuren and colleagues [10] in classic studies reported that externally measurable work was the primary determinant of myocardial oxygen consumption. Later in the same year, McKeever and coworkers [11] reported that the arrested heart consumed less oxygen than either the fibrillating or the beating nonworking heart in an isolated heart preparation. Further reduction in oxygen consumption was demonstrated in the studies by Fuquay and associates [12] in 1962 when they cooled the cardiac perfusate.

In 1960, Lower and Shumway [13] described the technique for orthotopic cardiac transplantation, and Barnard [14] accomplished the first operative success in orthotopic cardiac transplantation in humans in 1967. It was then obvious that if cardiac transplantation was to become a technology with wide clinical applicability, some method for ex vivo preservation of the heart would be mandatory. In 1966, Webb and associates [15] had described a technique using metabolic inhibitors to establish a state of "suspended animation" of the heart.

Stimulated by those events and encouraged by my mentors (W. C. Sealy, D. C. Sabiston, Jr, and P. A. Ebert), in 1968, as a surgical resident, I began a series of laboratory investigations with the goal of identifying a technique that would enable prolonged protection of the excised heart. Initial efforts using various types of perfu-

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Table 1. Composition of High-Potassium Solution Used to Induce Cardiac Arrest in Early Studies

Constituent	Amount (g/1,000 mL)
NaCl	4.0
KCl	2.5
Glucose	2.0
$NaHCO_3$	1.0

K = 25 mEq/L; pH = 7.5; Osmol = 275 ± 5 mosm/L.

sates and perfusion devices proved futile. In most of these studies, the isolated animal heart, probably because of overperfusion, became hemorrhagic and edematous and I was unable to assess either function or metabolism.

I put my investigations on "hold" while completing my surgical residency. I resumed them after joining the faculty at Cornell University Medical Center where, using an isolated, supported heart preparation, my colleagues and I evaluated the metabolic, functional, and morphological effects of potassium-induced cardioplegia [16]. In this study, we confirmed the earlier findings of McKeever and co-workers [11] demonstrating a fourfold decrease in oxygen consumption in the arrested heart compared with the beating, nonworking heart, the paced heart, and the fibrillating heart. A slight decrease in coronary vascular resistance was also observed in the arrested heart compared with the beating, paced, or fibrillating heart, but there was no difference in lactate extraction. Furthermore, the potassium-arrested heart tolerated 60 minutes of normothermic ischemia with only a mild reduction in ventricular function, whereas hearts subjected to 60 minutes of ischemia alone were not viable enough to have their function assessed. There was no histologically identified damage in the potassium-arrested hearts after 60 minutes of ischemia, but hearts subjected to ischemia alone had widespread necrosis. The cardioplegic solution used in those studies is shown in Table 1.

After finding that "switching off" the excitable membrane of the myocardial cell using hyperkalemia protected the heart from normothermic ischemia, we then attempted to document that the same principle could be applied to other excitable membranes during total-body circulatory arrest. In this study, groups of experimental animals were subjected to 15 minutes of complete circulatory arrest and were evaluated with respect to short-term survival (recovery from anesthesia) and brain levels of energy metabolites. None of the normothermic control animals awoke from anesthesia. All animals that received an infusion of high potassium solution and were kept at normothermia awoke, as did all animals cooled to 15°C, which indicates that both hypothermia and hyperkalemia may have a protective effect on the brain during total circulatory arrest. There was, however, no correlation between levels of high energy compounds in the brain and survival. The only clearcut difference was that the hypothermic group had higher glycogen levels, a difference probably due to the effect of low temperature on certain enzymes [17].

One of the more formidable challenges in cardiac surgery in the early 1970s was the successful performance of aortic valve replacement in elderly patients with heavily calcified valves and extreme degrees of left ventricular hypertrophy. The standard techniques of myocardial protection at that time included intermittent or continuous perfusion of the coronary arteries with blood from the pump oxygenator or use of topically applied hypothermia. In my experience, neither of these techniques proved entirely satisfactory. Therefore, hyperkalemic cardiac arrest was first tried in this group of patients. The results were most satisfying in that the technique resulted in establishment of a quiet and relatively bloodless operative field, did not require continuous or intermittent holding of a device in the coronary ostia and, most important, resulted in routine survival of the patients. We then began to use potassium cardioplegia routinely in other types of cardiac operations. The composition of the crystalloid cardioplegia used in most of these cases is as follows: to 1,000 mL of 5% dextrose in one-fourth normal saline is added 40 mEq KCl and 10 mEq $NaHCO_3$ (K = 40 mEq/L, pH 7.7; osmolarity = 320 mosm/L). This solution was later modified by reducing the potassium concentration to 20 mEq/L and reducing the added bicarbonate to 5 mEq. I used that crystalloid solution exclusively until 1984 with quite satisfactory results.

I would be remiss if I did not acknowledge the tremendous boost in confidence I obtained from reading the report by Kirsch and associates [18] in 1972 describing their clinical experience using a magnesium-based cardioplegic solution.

Many individuals in cardiac surgery continue to use crystalloid cardioplegia and, indeed, I use a modification of the crystalloid cardioplegic solution described for preservation of donor hearts to be transplanted. Most surgeons now use some form of blood cardioplegia as the method of choice. The studies of Follette [19], Barner [20], Catinella [21], and their associates clearly establish blood as the preferred delivery vehicle for cardioplegic agents. It is doubtful, however, that the final chapter in myocardial preservation has been written. The description of a reperfusion injury has created a new challenge. Moreover, the efficacy of other additives to cardioplegic solutions (osmotic agents, local anesthetic agents, other cations, corticosteroids, glucose, insulin, calcium channel blockers, various metabolic intermediates) remains to be evaluated thoroughly. There can be no doubt that intraoperative myocardial protection is much more effective now than it was 20 years ago, and unquestionably it has contributed to the lowering of mortality rates in cardiac surgery.

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Pulmonary Artery Banding: Analysis of a 25-Year Experience

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A 25-year experience (May 1962 through April 1987) with pulmonary artery banding in 183 patients was reviewed and analyzed. Pulmonary artery banding was performed in a heterogenous group of patients aged two days to 60 months (median, 10 weeks; mean, 21.8 weeks) and weighing 1.4 to 13.8 kg (mean, 4.2 kg). Diagnosis was ventricular septal defect in 76 (41.5%) and atrioventricular communis in 41 (22.4%). Pulmonary artery banding was also used in patients with d-transposition of the great vessels with ventricular septal defect, double-outlet right ventricle, univentricular heart, tricuspid atresia, and truncus arteriosus. Early death occurred in 39 of 175 patients who underwent pulmonary artery banding at Ochsner Foundation Hospital (22.3%). Definitive operation has been performed in 37 of the patients who underwent pulmonary artery banding since 1979 with excellent outcome in 32 (86.5%). Pulmonary artery banding is a useful palliative procedure for a diverse group of patients with congenital cardiac anomalies and unrestricted pulmonary blood flow. With improved results of primary repair of intracardiac anomalies in small infants, however, pulmonary artery banding should be reserved for severely ill patients with complex lesions not amenable to early definitive correction. Currently, pulmonary artery banding is indicated in patients with excessive pulmonary blood flow and single ventricle or tricuspid atresia. Pulmonary artery banding is also appropriate in certain patients with atrioventricular communis and in patients with muscular or multiple ventricular septal defects. Pulmonary artery banding is an option in patients with ventricular septal defect and coarctation of the aorta.

(Ann Thorac Surg 1989;48:444–50)

Pulmonary artery (PA) banding was first used clinically by Muller and Dammann [1] in 1951. Over the next decade, techniques for definitive correction of congenital intracardiac defects became available [2–4]. Because of the high mortality associated with cardiopulmonary bypass in small infants, however, palliative PA banding was used initially, with definitive anatomical correction at an older age [5]. In recent years, there has been a trend to proceed with definitive repair of intracardiac lesions in younger and smaller children.

Pulmonary artery banding has been performed at Ochsner Foundation Hospital since 1962. We review a 25-year experience with PA banding and analyze the changing role of this procedure in the management of infants with congenital cardiac malformations manifested by excessive pulmonary blood flow and pulmonary hypertension.

Material and Methods

Patient Population

From May 1962 through April 1987, 175 patients underwent PA banding at the Ochsner Foundation Hospital. During this period, 7 other patients had definitive operations, and 1 patient underwent a palliative procedure subsequent to PA banding elsewhere. All patients with PA bands seen through April 1987 are included. Clinic and hospital records were reviewed retrospectively. Late follow-up was obtained through December 1987.

Before PA banding, all patients underwent diagnostic cardiac catheterization and angiography. Since October 1981, high-resolution two-dimensional echocardiography has also been used routinely.

Procedure

The PA band was made from strips of woven Dacron 3 to 7 mm wide (a narrower band was used in cases of unilateral or individual-bilateral PA banding). Since 1970, PA bands have been coated with silicone to facilitate later removal. The band was sutured to the wall of the PA to prevent distal migration. In general, the adequacy of PA constriction was determined intraoperatively by measurement of distal PA pressure. However, at the surgeon's discretion, pressure measurements were omitted after inspection and palpation of the banded PA. Complete reevaluation was performed in all patients with PA bands before subsequent definitive or palliative operations; in most cases, this included repeat cardiac catheterization and angiography.

Results

Pulmonary artery banding was performed in 88 male and 95 female patients with an age range of two days to 60

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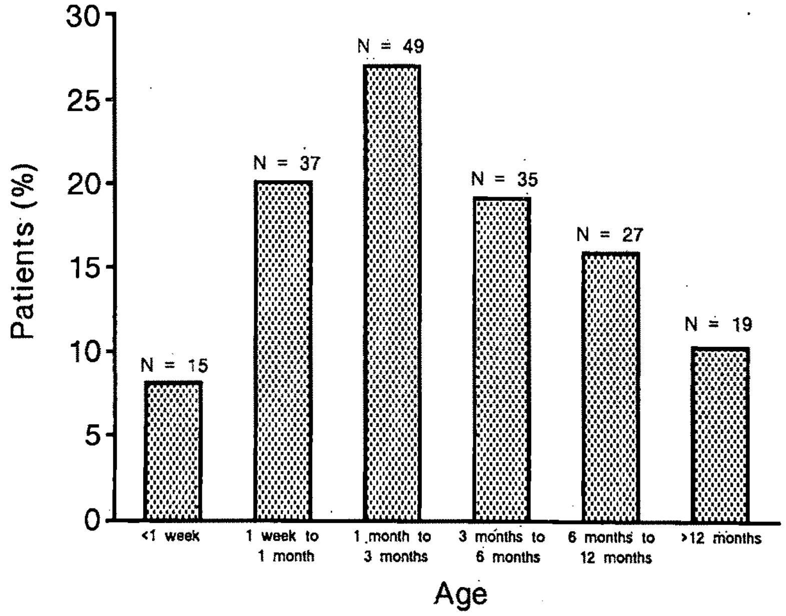


Fig 1. Age at pulmonary artery banding.

months (median age, 10 weeks; mean age 21.8 ± 2.7 [standard error] weeks). Fifteen patients (8.2%) were aged less than 1 week, and 52 (28.4%) were aged less than 1 month. Nineteen patients (10.4%) were aged more than 1 year at the time of PA banding (Fig 1). In the past 5 years, no PA bands were placed in children aged more than 1 year. Weight at PA banding was 1.4 to 13.8 kg (mean weight, 4.2 ± 0.2 kg). Most of these children had severe failure to thrive (Fig 2).

The indication for PA banding was excessive pulmonary blood flow with pulmonary hypertension and heart failure. The primary anatomical diagnoses are shown in Figure 3. All patients with the diagnosis of atrioventricular communis (AVC) had marked deficiencies of the ventricular septum (ie, complete form of AVC). The circumstances of PA banding in patients with the diagnosis "other" are shown in Table 1. Ninety-nine patients (54.1%) had additional cardiovascular anomalies. These included patent ductus arteriosus (PDA) in 81 (44.3%), coarctation of the aorta in 26 (14.2%), interrupted aortic arch in 18 (9.8%), and atrial septal defect in 19 (10.4%). Patients who recently had PA banding for ventricular septal defect (VSD) were smaller and had more complex anatomical and physiological problems (Table 2).

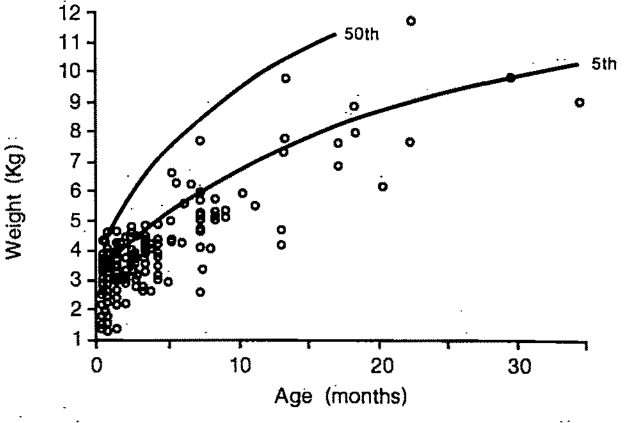


Fig 2. Weight at pulmonary artery banding. Patients are compared with normal females at the 5th and 50th percentile.

Table 1. Circumstances of Pulmonary Artery Banding in Patients With Diagnosis of "Other"

Circumstances	No. of Patients	Comment
Unilateral pulmonary hypertension with contralateral pulmonary ischemia	2	Both patients underwent unilateral PA banding[a]
Preparation for arterial switch procedure in patients with TGV and intact ventricular septum	2	One patient underwent a Mustard operation 41 months later with good outcome. The other patient died 37 months after banding.
Error in preoperative diagnosis	3	All of these patients were examined before two-dimensional echocardiography was used. These patients had severe PA hypertension[b] and were believed to have a VSD. All 3 patients died within 30 days of operation. At autopsy, the ventricular septum was intact in all 3. Two had cardiomyopathies and 1 had mitral stenosis.

[a] See Table 3. [b] Mean systolic PA pressure was 94 mm Hg in these 3 patients.

PA = pulmonary artery; TGV = d-transposition of the great vessels; VSD = ventricular septal defect.

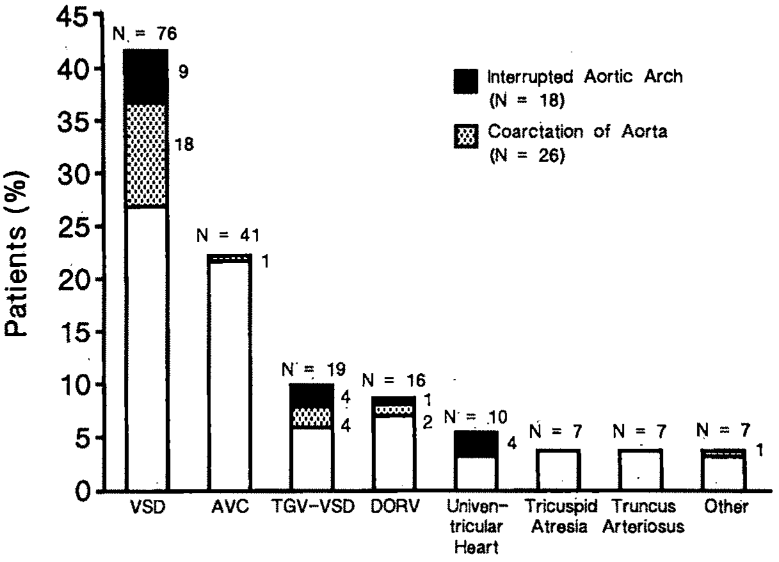


Fig 3. Diagnosis in patients who underwent artery banding. Coarctation of the aorta or interrupted aortic arch was present in 44 of 183 patients (24.0%). (AVC = atrioventricular communis; DORV = double-outlet right ventricle; TGV-VSD = d-transposition of the great vessels with ventricular septal defect; VSD = ventricular septal defect.)

Banding of the main PA was performed in 176 patients (96.2%). Systolic PA pressure before banding was 80.5 ± 1.8 mm Hg, and systolic PA pressure after banding was 46.1 ± 1.3 mm Hg. The decrease in PA pressure with banding was 41.4% ± 1.8%. Systolic PA pressure at the time of definitive operation was 38.0 ± 2.3 mm Hg (Fig 4). The ratio of systolic PA pressure to systemic pressure was 0.53 ± 0.02 immediately after banding and 0.40 ± 0.05 at the time of definitive operation. Unilateral or individual-bilateral PA banding was performed in 7 patients (3.8%) when main PA banding was not feasible (Table 3). Simultaneous procedures were performed in 101 patients (55.2%) (Table 4).

Complications related to the tightness or position of the band occurred in 44 patients (24%) (Table 5). Other complications included hemorrhage during placement of the band in 1 patient (successfully controlled) and pericardial fluid collections requiring surgical drainage in 2 patients. In 5 patients, a VSD closed spontaneously.

Follow-up is complete in 166 of the 183 patients (90.7%) (Table 6). The mean follow-up period is 51.6 ± 4.5 months; 1 patient has been followed for 22 years since PA banding. Early death occurred in 39 of 175 patients (22.3%) who underwent PA banding at Ochsner Foundation Hospital. This includes 36 deaths within 1 month of operation as well as 3 late hospital deaths (56 to 60 days after operation). Diagnoses in this group of patients are shown in Fig 5. Eighteen of the 39 patients (46.1%) had some form of obstruction to left ventricular outflow: coarctation of the aorta in 8 (20.5%) and interrupted aortic arch in 10 (25.6%). Conversely, there were eight deaths among the 26 patients who had coarctation of the aorta (30.8%) and ten deaths among the 18 patients with an interrupted aortic arch (55.6%). In the 131 patients with unobstructed left ventricular outflow, there were 21 early deaths (16.0%).

Table 2. Comparison of Patients Who Underwent Pulmonary Artery Banding for Ventricular Septal Defects During the First 100 Months and Most Recent 100 Months of the Series

Variable	May 1962 to August 1970	January 1979 to April 1987
No. of patients	18	35
Age (wk)[a]	27.5 ± 8.5	15.7 ± 5.9
Weight (kg)[a]	4.7 ± 0.4	3.6 ± 0.3[b]
Coarctation of the aorta[c]	2 (11.1)	9 (26.5)
Interrupted aortic arch[c]	0	7 (20.0)
Patent ductus arteriosus[c]	3 (16.6)	20 (57.1)[d]
Multiple VSDs[c]	0	2 (5.7)

[a] Mean ± SE. [b] $p = 0.05$ by Student's t test. [c] Numbers in parentheses are percentages. [d] $p = 0.01$ by χ^2 analysis.

VSD = ventricular septal defect.

One hundred five patients (57.4%) have had or are currently awaiting definitive surgical repair. Among 89

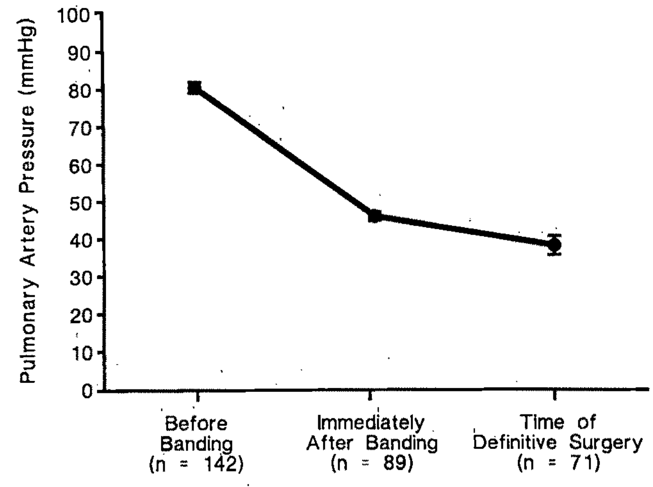


Fig 4. Changes in pulmonary artery (PA) pressure with banding of the main pulmonary artery. Systolic PA pressure before banding was 80.5 ± 1.8 mm Hg, and systolic PA pressure after banding was 46.1 ± 1.3 mm Hg. Systolic PA pressure at the time of definitive operation was 38.0 ± 2.3 mm Hg.

Table 3. Unilateral and Individual-Bilateral Pulmonary Artery Banding

Diagnosis	No. of Patients	Comment
Unilateral PA banding		
DORV, hypoplastic left PA	1	Unilateral right pulmonary hypertension. Contralateral PA hypoplasia resulted in acceptable perfusion of the left lung. Pulmonary hypertension precludes definitive operation.[a]
Single ventricle, stenosis of main PA and left PA, previous anastomosis of right PA to aorta[b]	1	Unilateral pulmonary hypertension with contralateral pulmonary ischemia.[c] Pulmonary hypertension precludes definitive operation.[a]
Ventricular and atrial septal defects, PDA, atresia of right PA	1	Unilateral pulmonary hypertension with contralateral pulmonary ischemia.[c]
Truncus arteriosus, atresia of left PA	1	Early death.
Individual-bilateral PA banding		
Truncus arteriosus (type II)	2	Early death.
Single ventricle, hypoplastic aortic arch	1	Previous operation for jejunal atresia. Early death.

[a] See Table 7. [b] This operation was performed elsewhere. The right pulmonary artery was divided and a side-to-end aortopulmonary anastomosis was performed. [c] Primary diagnosis: Other. See Table 1.

DORV = double-outlet right ventricle; PA = pulmonary artery; PDA = patent ductus arteriosus.

patients who have undergone PA banding since 1979, 37 have subsequently undergone definitive operation, with excellent outcome in 32 (86.5%). Four patients (2.2%) have complex anomalies not amenable to definitive repair; all these patients have required further palliative procedures. Three patients (1.6%) have severe pulmonary hypertension precluding further repair; 2 of these patients had unilateral PA banding. One patient was referred at 18 months of age with an isolated VSD. Unfortunately, her severe pulmonary hypertension persisted despite PA banding (Table 7).

Table 4. Procedures Performed at Same Operation as Pulmonary Artery Banding

Procedure	No. of Patients[a]
Ligation of patent ductus arteriosus	83 (45.4)
Correction of coarctation of the aorta	18 (9.8)
Correction of interrupted aortic arch	16 (8.7)
Atrial septectomy	10 (5.5)
Lung biopsy	4 (2.2)
Other	2 (1.1)
Total No. of patients with additional procedures performed at time of pulmonary artery banding	101 (55.2)

[a] Numbers in parentheses are percentages of 183 patients.

Table 5. Complications Related to Tightness or Position of the Pulmonary Artery Band

Complication	No. of Patients[a]
Band required revision	8 (4.4)
Definitive operation necessary within 1 year[b]	5 (2.7)
Persistent pulmonary hypertension[c]	27[d] (14.7)
Distal migration	9 (4.9)
Total No. of patients with complications related to tightness or position of band[e]	44 (24)

[a] Numbers in parentheses are percentages of 183 patients. [b] Definitive operation was deemed necessary because of persistent or recurrent heart failure refractory to medical therapy. [c] Systolic pulmonary artery pressure greater than or equal to 60 mm Hg or greater than or equal to 60% of systemic pressure at time of recatheterization, or both. [d] Two of these patients had unilateral pulmonary artery banding. In both, pulmonary hypertension precludes definitive operation. See Table 7. [e] Five patients had two of these complications.

Comment

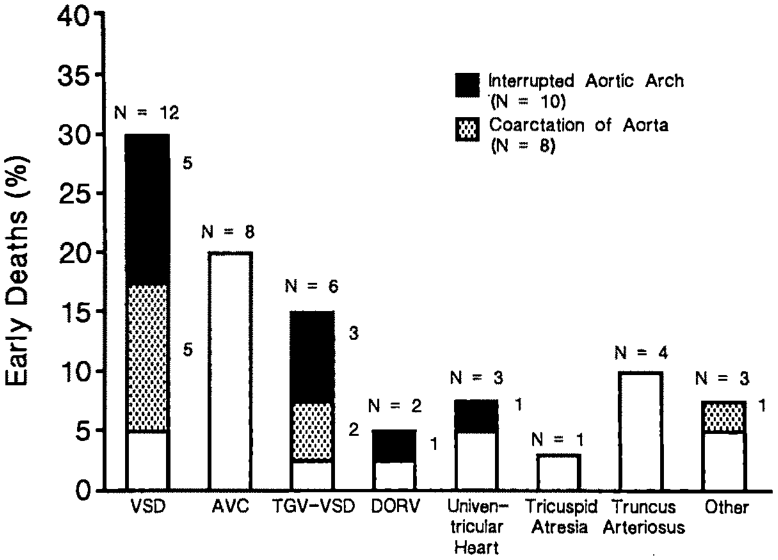
A 25-year experience with PA banding in a single institution was reviewed and analyzed. Pulmonary artery banding has been used as a palliative procedure in patients with a variety of congenital cardiac anomalies [6–10]. The ideal role of PA banding requires ongoing reassessment, however. Whereas PA banding was at one time frequently used in patients with uncomplicated VSD [5, 6],

Table 6. Follow-up After Pulmonary Artery Banding

Endpoint	No. of Patients[a]
Early death	39 (22.3)[b]
Late death	15 (8.2)
Definitive operation	89 (48.6)
Awaiting definitive operation	16[c] (8.7)
Not suitable for definitive repair	4 (2.2)
Pulmonary hypertension precluding definitive repair[d]	3 (1.6)
Lost to follow-up	17 (9.3)

[a] Numbers in parentheses are percentages. [b] This figure represents early mortality among 175 patients who underwent initial pulmonary artery banding at Ochsner Foundation Hospital. All other percentages are based on the entire group of 183 patients. [c] One of these patients is currently being treated for acute lymphoblastic leukemia. Her cardiovascular status is good 5 years 6 months after pulmonary artery banding, and definitive repair will await the outcome of treatment for leukemia. [d] See Table 7.

Fig 5. Diagnosis in patients who died early after pulmonary artery banding. Coarctation of the aorta or interrupted aortic arch was present in 18 of the 39 patients who died (46.1%). (AVC = *atrioventricular communis;* DORV = *double-outlet right ventricle;* TGV-VSD = *d-transposition of the great vessels with ventricular septal defect;* VSD = *ventricular septal defect.)*



today early definitive repair is generally performed at our institution and elsewhere [9–11]. The role of PA banding in VSD associated with coarctation of the aorta is less clear [10]. Problems associated with this approach include increased difficulty and risk of subsequent definitive operation, and spontaneous closure of the VSD in a number of patients necessitating subsequent operation solely to remove the band. Consequently, repair of the coarctation without PA banding is advocated [12]. Another approach is repair of both coarctation and VSD at the same operation using either median sternotomy [13] or thoracotomy followed by median sternotomy [14]. According to Kirklin and Barratt-Boyes [15], the indication for PA banding for primary VSD is limited to severe heart failure in patients with Swiss-cheese septum, or severe coarctation of the aorta in the first 2 months. When PA banding is required at the time of coarctation repair, early definitive operation (2 to 3 months) should be performed.

The treatment of AVC, and particularly the role of PA banding, is controversial. The marked morphological variability within the group of patients considered to have complete AVC hampers analysis and comparison of various methods of therapy [16]. Pulmonary artery banding has been recommended as the initial surgical procedure in infants with AVC, with early mortality rates of 4.7% to 30% [17, 18]. However, primary repair of this defect within the first year is advocated by Bender and associates [19] based on good outcome in 21 of 24 patients. Despite the trend toward early definitive repair of AVC defects, PA banding is the preferred approach in seriously ill infants with right or left ventricular hypoplasia [20, 21].

The surgical management of d-transposition of great vessels with VSD and double-outlet right ventricle and subpulmonary VSD is undergoing rapid evolution. Quaegebeur and co-workers [22] reported an early mortality of 16% in 43 patients who underwent an arterial switch procedure for these anomalies in an 8-year period. Most important, the results improved with time, and the actuarial 1-year survival for patients operated on in 1985 was 99.7%. These investigators concluded that PA banding

Table 7. Patients with Pulmonary Hypertension Precluding Definitive Operation

Diagnosis	Type of Banding	Age at Banding (mo)	Comment
DORV, hypoplastic left PA	Unilateral banding of right PA	2	At age 11 years, PA pressure was 103/50 mm Hg.
Single ventricle, stenosis of main PA and left PA, previous anastomosis of right PA to ascending aorta[a]	Unilateral banding of right PA	45	Biopsy of right lung at time of banding with changes of pulmonary hypertension (grades 3 and 4[b]).
Ventricular septal defect	Main PA banding	18	PA pressure before banding was 100/51 mm Hg. PA pressure 5 years later was 127/65 mm Hg. Patient attends high school but has dyspnea on exertion.

[a] This operation was performed elsewhere. The right pulmonary artery was divided, and a side-to-end aortopulmonary anastomosis was performed.
[b] Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease. A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 1958;18:533–47.

DORV = double-outlet right ventricle; PA = pulmonary artery.

was not indicated regardless of age or size. However, others [9, 10] continue to prefer initial PA banding with delayed definitive operation for d-transposition of the great vessels with VSD and double-outlet right ventricle. Because the results of early anatomical repair of d-transposition of the great vessels with intact ventricular septum are very good [22], there is no indication for initial PA banding followed by late arterial switch.

Pulmonary artery banding for truncus arteriosus has been associated with multiple problems and high mortality. Positioning of the band proximal to the PA bifurcation (type I) frequently results in unequal narrowing of the two branches, with marked imbalance in pulmonary perfusion [23]. Individual-bilateral PA banding has also been unsatisfactory, with a high rate of complications [10]. The results of definitive repair are currently good, and this is the preferred approach for this anomaly [24]. At Ochsner Foundation Hospital, only 1 patient has had PA banding for truncus arteriosus in the past 10 years.

The usefulness of PA banding has been questioned, and its role is currently limited in the management of the anomalies discussed in this report. However, there is still an important place for PA banding in infants with either single ventricle or tricuspid atresia and unrestricted pulmonary blood flow. Definitive surgical management of these anomalies by a Fontan-type procedure is performed between the ages of 1 and 5 years [15]. Pulmonary artery banding is particularly valuable in preventing alterations in pulmonary vascular resistance, which could preclude ultimate surgical repair. A major problem with PA banding in single ventricle and tricuspid atresia is the development of severe outflow chamber obstruction associated with spontaneous closure of the VSD. Attempts to correct this problem have been associated with a high mortality [15].

Pulmonary artery banding in patients with left ventricular outflow obstruction requires special consideration. This situation is complex in that after banding biventricular outflow obstruction exists in varying degree. In this series, 18 of the 39 patients (46.1%) who died early had some form of obstruction to left ventricular outflow, and the early mortality rate for patients who had left ventricular outflow obstruction was 40.9%, as compared with early mortality of 16.0% in patients with unrestricted left ventricular outflow. The role of PA banding in patients with coarctation of the aorta associated with VSD has been discussed. When associated with complex intracardiac defects, coarctation of the aorta has a poor outcome, with 5-year survival as low as 40% [25]. Goldman and associates [12] recommend PA banding, at the time of coarctation repair, in patients with associated complex intracardiac lesions. In patients with an interrupted aortic arch, reconstruction of the aorta with simultaneous PA banding has been recommended [26]. High mortality with this technique has led to other approaches, however. Hammon and co-workers [27] recommend direct reconstruction of the aortic arch and repair of the intracardiac defects using a median sternotomy and hypothermic circulatory arrest. When the aortic interruption is associated with subaortic stenosis, insertion of a graft from the proximal PA to the descending aorta with banding of the distal main PA is preferred by Ilbawi and associates [28].

Pulmonary artery banding requires great care and technical precision. The PA band must be tight enough to reduce PA blood flow and alleviate pulmonary congestion. However, it should not cause pulmonary hypoperfusion, and it must be loose enough to allow for growth before definitive operation. The band should remain between the pulmonary valve and the bifurcation of the PA. In a group of 38 long-term survivors, Mahle and associates [8] documented problems with tightness of the band in 12% and position of the band in 37%. A method for determining optimum band circumference (Trusler's rule) has been developed [9]. According to this method, the estimated circumference for a PA band in patients with a VSD without bidirectional intracardiac shunting is 20 + 1 mm for each kilogram of body weight. For patients with a VSD and bidirectional intracardiac shunting, the estimated band circumference is 24 + 1 mm for each kilogram of body weight. The problem of determining and maintaining appropriate tightness of PA bands has stimulated the development of bands that can be adjusted without reoperation [29–31].

Careful analysis of the results of PA banding is essential. The adequacy of PA banding can be readily evaluated by two-dimensional echocardiography [32]. To achieve the best possible outcome, unsatisfactory PA bands should be revised in the early postoperative period.

Pulmonary artery banding is a useful palliative procedure for a diverse group of congenital cardiac anomalies. With improved results of early definitive repair of intracardiac defects in young infants, however, PA banding should be reserved for severely ill patients with complex lesions not amenable to early primary repair. Currently PA banding is indicated in patients with excessive pulmonary blood flow and single ventricle or tricuspid atresia. Pulmonary artery banding is also appropriate in certain patients with AVC and in patients with muscular or multiple VSDs. Pulmonary artery banding is an option in patients with VSD and coarctation of the aorta.

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Cardiac Neoplasms

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CORRESPONDENCE

Can Ventricular Decompression Be Optimized?

To the Editor:

The use of the Pierce-Donachy ventricular assist device in patients with cardiogenic shock after a cardiac operation as described by Pennington and associates [1] continues to be an important contribution to the management of a difficult group of patients. In their comments on this series, Pennington and associates state that "ventricular recovery can occur without complete decompression"; the implication is that the object of ventricular assist is to reduce ventricular end-diastolic pressure to the lowest level possible, if not to zero.

It is my impression that "complete decompression" of the left ventricle is undesirable for several reasons. (1) Complete decompression may cause the interventricular septum to shift to the left, thereby impairing right ventricular ejection and precipitating right ventricular failure [2, 3]. (2) Complete decompression may, over a period of time, cause deconditioning of the bypassed ventricle and delay functional recovery [4]. (3) Peak systolic subendocardial pressure has been demonstrated to exceed coronary perfusion pressure even in the empty beating heart and has been associated with increased myocardial oxygen consumption [5].

With these considerations in mind, I should like Pennington and associates to (1) define "complete ventricular decompression" and (2) suggest whether or not, in their experience, one can actually select an "optimal" amount of ventricular decompression that will preserve right ventricular function, prevent deconditioning of the bypassed ventricle, and reduce myocardial oxygen consumption.

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Reply

To the Editor:

Dr Lee raises several important questions about the role of "complete decompression" of the left ventricle by ventricular assist devices in patients with cardiogenic shock. The "complete ventricular decompression" referred to in our paper describes the situation in which there is no ventricular ejection during left ventricular systole. It is well recognized that this state does not profoundly reduce left ventricular myocardial oxygen consumption. However, there is evidence that the degree of decompression may allow more rapid recovery of the acutely infarcted ventricle [1, 2]. Although interventricular septal shifts do occur with left ventricular decompression in experimental animals, these changes have not been shown clinically to induce right ventricular failure in patients [3]. It is our impression that a normal right ventricle cannot be made to fail under such circumstances, unless there is an increase in pulmonary vascular resistance [4]. The idea that "complete decompression" over longer periods of time (greater than 2 weeks) may lead to myocardial atrophy is an interesting but unproven theory. We have documented rather marked decreases in left ventricular function in several patients we have maintained on left ventricular assist devices for more than 50 days. However, the cause of the diminished function is not entirely clear. Although some degree of "myocardial atrophy" may have occurred, some of the patients clearly sustained myocardial infarctions during the period of support. We are currently preparing a manuscript describing these pathological findings.

Unfortunately, at this time, we are unable to define the optimal degree of ventricular decompression that will allow myocardial recovery. We believe this is an important aspect of mechanical circulatory support that needs much more investigation.

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Bleeding and Anticoagulation

To the Editor:

I read with interest the panel discussion on bleeding and anticoagulation from the Circulatory Support 1988 meeting [1]. Contrary to the information of Dr Joist, my colleagues and I have several publications relating to the assessment of and the treatment of excessive post-pump bleeding employing Amicar and appropriate components [2–5]. Those publications also brought attention to the fact that platelet therapy lacked clinical and statistical relevance despite demonstrable abnormalities in terms of platelet numbers and platelet assessment functions. The articles embraced the acceptance of an asanguineous prime, hemodilution, and the acceptance of normovolemic anemia postoperatively. Throughout the prospective period of study, autotransfusion and the collection of "shed" blood was also practiced.

Today, in our cardiovascular program as well as in our transplant services, we continue to believe that hyperfibrinolysis is the

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predominant cause of excessive bleeding, that its assessment can be meaningfully done, and that treatment can be specifically directed. We take issue with those who contend that the prothrombin time, the partial thromboplastin time, and the activated total clotting time have an a priori relevance in terms of assessment because they are universally distorted by the presence of heparin or heparinlike substances (hyperlipemia).

Before any meaningful assessment can be done, the presence or absence of heparin must be clearly established, the fibrinogen level must be determined, and a decision must be made as to whether there is an associated derangement in the intrinsic pathway or the extrinsic pathway of the clotting cascade. Only then can one determine whether the need is for Amicar alone or for Amicar plus intrinsic (cryoprecipitate) as contrasted with extrinsic (fresh frozen plasma) clotting factor supplementation.

Although they are not yet published, my colleagues and I have done postoperative studies using radioactive iodine that demonstrate no difference whatsoever with respect to the incidence of peripheral thrombophlebitis among patients managed with no Amicar, no components, with Amicar, and with Amicar plus components after operation.

I am certain that any primary deficiency of others to have benefited is due to a failure to render a sufficient dose of Amicar and that the concerns about hypercoagulability are overstated. In an area embracing several different institutions, with a variety of clotting support systems, I bring attention to the fact that accurate testing, rapidity of retesting, and the ready availability of the products in the immediate postoperative period are decidedly essential for the efficacy of our endeavors. Likewise, attention should be directed to the fact that no type of preoperative coagulational screening was found helpful aside from a history of "free bleeding tendencies."

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Left Ventricular Rupture

To the Editor:

I read with interest two recent articles [1, 2] and an editorial [3] about rupture of the left ventricle after mitral valve replacement. In all three, the etiology of this devastating complication is reviewed.

I have not found described yet a mechanism that may produce disruption of the atrioventricular groove (type I) after implantation of a mitral valve: rotation of a mechanical prosthesis.

When a tilting-disc prosthesis is inserted and movement of the disc is impaired by structures in the left ventricular cavity, it can be rotated to obtain the optimal opening angle. If this rotation is done when all the sutures have been tied and no effective countertraction is applied to the sewing ring, the tangential forces over the annulus may disrupt the atrioventricular junction. I have seen this complication occur on two occasions with deadly results.

Ways of preventing this occurrence include adequate sizing of the prosthesis, trimming of papillary muscles to allow free movement of the disc, and, if the disc is still impaired, rotation of the housing before the sutures are tied down, holding the sewing ring steadily during the maneuver.

I congratulate the authors for bringing up the subject and I hope that this letter may alert surgeons to one more cause of left ventricular wall rupture after mitral valve replacement.

Alejandro Aris, MD

Cardiac Surgery Unit
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1. Azariades M, Lennox SC. Rupture of the posterior wall of the left ventricle after mitral valve replacement: etiological and technical considerations. Ann Thorac Surg 1988;46:491–4.
2. Karlson KJ, Ashraf MM, Berger RL. Rupture of left ventricle following mitral valve replacement. Ann Thorac Surg 1988;46:590–7.
3. Rainer WR. Rupture of left ventricle following mitral valve replacement [Editorial]. Ann Thorac Surg 1988;46:488.

Reply

To the Editor:

Although an extensive review of the literature and a survey of our own experience failed to uncover a single instance of disruption of the annulus from rotation of the prosthesis during mitral valve replacement, we do not doubt that such a disaster can occur. The most likely mechanism is application of excessive or sudden force during the maneuver.

As far as preventive measures are concerned, we agree with Dr Aris that the insertion of an oversized prosthesis invites rupture of the left ventricle and indeed mentioned this fact in our article. However, we are reluctant to support the concept that radical trimming of the papillary muscles is desirable, as vigorous resection is thought to be responsible for most type II ruptures and therefore should be avoided. Furthermore, even if disc motion appears to be limited by the stump of the papillary muscle in the paralyzed heart it is most unlikely that this problem will persist once the organ resumes function. In the working state, as the ventricle fills with blood, the free wall stretches and the papillary muscles retract, so that contact between the stump and the disc is unlikely. Finally, the possibility of papillary muscle interference with disc motion is obviated by retaining the native valve. We cited in our review convincing evidence from the literature that retention of the native valve preserves structural and functional integrity of the left ventricle, which in turn is associated with a reduced incidence of rupture and dysfunction of the left ventricle. Dr Aris' experience adds a new incentive for retaining the valvular apparatus during mitral valve replacement.

We agree with the suggestion that rotation of the disc is preferable prior to tying the fixation sutures in order to prevent torsion and disruption of the annulus. However we would also like to note that stabilization of the sewing ring for safe rotation of the disc is possible even after the sutures are tied. This can be accomplished by the application of two clamps onto the sewing ring, 180 degrees apart. The rotational force, however, should not be excessive or sudden. It must be gentle and gradual.

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Mian M. Ashraf, MD

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Use of Colostomy Bags for Chest Tube Drainage

To the Editor:

We read with interest the article by Velanovich and Adams [1] on the use of colostomy bags for chest tube drainage. We have been using these bags for the last 3 years and we fully agree that such use reduces the hospital stay and increases the mobility of patients.

We want to point out that it is important for the colostomy bag to have an opening at the top so that the air can escape; otherwise, a patient with bronchial air leak might develop tension pneumothorax. This is an important fact that was not emphasized in the article.

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Reference

1. Velanovich V, Adams CW. The use of colostomy bags for chest tube drainage. Ann Thorac Surg 1988;46:697–8.

Reply

To the Editor:

We agree that when using a closed system such as a colostomy bag for drainage of the pleural space, a bronchopleural air leak will lead to a pneumothorax. An opening at the top of the colostomy bag may remedy this problem. We have never had the opportunity to treat a patient with a bronchopleural air leak with the colostomy bag drainage system we have described. We feel that the indications for the colostomy system in such a patient are limited.

Vic Velanovich, MD
Carl W. Adams, MD

Department of Surgery
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Value of Transesophageal Echocardiography During Open Heart Operation

To the Editor:

The use of two-dimensional transesophageal echocardiography during open heart procedures is becoming increasingly popular [1]. We report a patient in whom two-dimensional transesophageal echocardiography disclosed a thrombus in the left atrium after a mitral-aortic valve operation, allowing the prevention of a possible life-threatening systemic embolism.

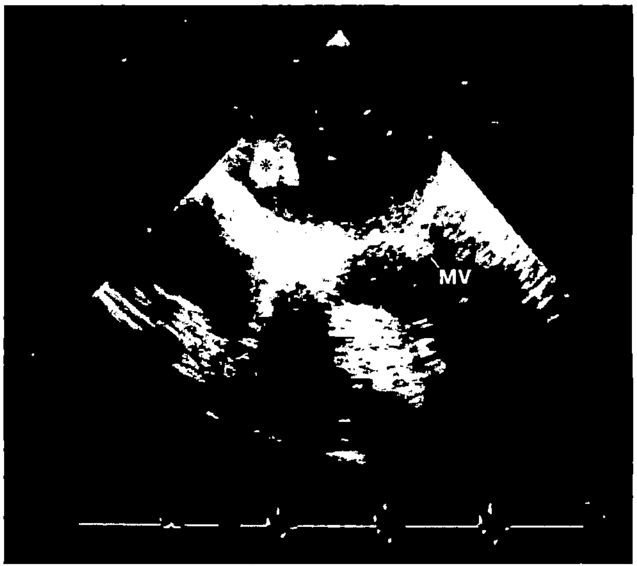

Fig 1. Transesophageal echocardiographic scanning (longitudinal view) showing a left atrial mass (asterisk) *close to the atrial septum and a few centimeters above the mitral valve* (MV).

A 62-year-old man with mitral and aortic stenosis was referred to our unit for surgical treatment. At operation, performed in January 1989, open mitral commissurotomy with splitting of the papillary muscles and aortic valve replacement with a 25-mm Pericarbon bioprosthesis (Sorin Biomedica, Saluggia, Italy) were performed. Direct inspection failed to demonstrate any thrombus in either the left atrium or the left atrial appendage. At the end of the procedure air bubbles were removed from the heart using standard techniques, which included cardiac massage and vigorous inflation of the lungs.

After release of the aortic cross-clamp the heart resumed spontaneous activity but was kept unloaded during completion of rewarming. At this stage two-dimensional transesophageal echocardiography, employed with the aim of evaluating the success of mitral valve repair, showed the unexpected presence of a mobile mass in the left atrium, which was interpreted as a thrombus (Fig 1). Rewarming was then interrupted, the aorta was cross-clamped, and the heart was again arrested with crystalloid cardioplegia. The right atrium was opened and the left atrium was entered through the fossa ovalis. By this approach a free floating thrombus, most likely previously dislodged into a pulmonary vein, was noted and removed. The procedure was then completed uneventfully and the patient was discharged on postoperative day 8 in good condition.

The intraoperative use of two-dimensional transesophageal echocardiography has proved effective in the evaluation of left ventricular contractility after coronary bypass operations, in the assessment of adequacy of valve repair techniques, and in the detection of intracardiac air bubbles before discontinuation of cardiopulmonary bypass [1–3]. We report here a patient in whom the presence of a thrombus in the left atrium, which had escaped initial intracardiac inspection and would have most likely resulted in systemic embolization, was diagnosed by two-dimensional transesophageal echocardiographic monitoring allowing an uncomplicated outcome. We believe that this experience supports the current trend of expanded use of two-dimensional transesophageal echocardiography during open heart procedures.

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1. Seward JB, Khandheria BK, Oh JK, et al. Transesophageal echocardiography: technique, anatomic correlations, implementation and clinical applications. Mayo Clin Proc 1988; 63:649–80.
2. Abel MD, Nishimura RA, Callahan MJ, Rehder K, Ilstrup DM, Tajik AJ. Evaluation of intraoperative transesophageal two-dimensional echocardiography. Anesthesiology 1987;66:64–8.
3. Dahm M, Iversen S, Schmid FX, Drexler M, Eberl R, Oelert H. Intraoperative evaluation of reconstruction of the atrioventricular valves by transesophageal echocardiography. Thorac Cardiovasc Surg 1987;35:140–2.

Adjustable Annuloplasty for Tricuspid Insufficiency

To the Editor:

In reply to the letter of Dr Julio Davila [1], we are pleased to see that the report of our technique of adjustable annuloplasty for tricuspid insufficiency [2] continues to generate interest as well as to evoke a more complete surgical history of the annuloplasty technique.

We note with interest the concerns expressed by Dr Davila regarding suture migration and annular laceration. In fact, although suture failure has been reported with the DeVega tricuspid annuloplasty technique [3, 4], such reports have indeed been rare even in large follow-up series [5, 6]. We have yet to see such a case. Such phenomena might more likely be anticipated with the higher pressure left-sided mitral lesions than with the lower pressure tricuspid mechanism, especially if an adequate correction of left-sided lesions can be accomplished.

Certainly Dr Davila's "furling" suture technique may provide a useful alternative in cases of extreme pulmonary hypertension, or in situations in which the tissue integrity of the tricuspid annulus is in doubt. For most situations, however, adjustable tricuspid annuloplasty remains a highly successful, rapid, and reproducible technique for preservation of valvular function and control of secondary tricuspid insufficiency.

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1. Davila J. Adjustable annuloplasty for tricuspid insufficiency [Letter]. Ann Thorac Surg 1989;47:639–40.
2. Kurlansky P, Rose EA, Malm JR. Adjustable annuloplasty for tricuspid insufficiency. Ann Thorac Surg 1987;44:404–6.
3. DeVega NG. Discussion of: Grondin P, Meere C, Liment R, et al. Carpentier's annulus and DeVega's annuloplasty. J Thorac Cardiovasc Surg 1975;70:859–60.
4. Nunez L, Celemin D, Iglesias A, et al. Rupture of the tricuspid valve associated with disruption of DeVega's annuloplasty. Chest 1981;79:111–3.
5. Grondin P, Meere C, Liment R, et al. Carpentier's annulus and DeVega's annuloplasty. J Thorac Cardiovasc Surg 1975; 70:852–61.
6. Chidambaram M, Abdulali SA, Baliga VG, et al. Long-term results of DeVega's tricuspid annuloplasty. Ann Thorac Surg 1987;43:185–8.

THE SOUTHERN THORACIC SURGICAL ASSOCIATION

Thirty-sixth Annual Meeting
November 9–11, 1989
The Phoenician Resort, Scottsdale, Arizona

The Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association will be held at The Phoenician Resort on November 9–11, 1989, with the Postgraduate Program on Thursday, November 9, from 7:45 AM to 12:00 noon. The meeting is open to all duly qualified physicians. Both members and nonmembers are urged to register in advance.

Registration and Fees

Advance registration forms, hotel reservation cards, and details regarding transportation arrangements will be mailed to Association members. Nonmembers should write to the Secretary-Treasurer, Gordon F. Murray, MD, The Southern Thoracic Surgical Association, 111 East Wacker Dr, Chicago, IL 60601.

Members are not required to pay a registration fee for the Scientific Program. Residents and fellows may register without payment of a registration fee upon presentation of a letter from their chief of service. The fee for other physicians is $155, except guest speakers, authors, and co-authors. Nurses and paramedical personnel may register upon payment of a $155 fee and presentation of a letter of introduction from a member.

Registration for the Postgraduate Program is $50 for all physicians, residents, and fellows.

Presentation and Publication

Papers presented at the Scientific Session must be submitted in triplicate to the Secretary-Treasurer, Gordon F. Murray, MD, at the time of presentation, or to the Editor of *The Annals of Thoracic Surgery* prior to presentation.

Speakers for the Regular Program are limited to 10 minutes; those in the Forum are limited to 5 minutes. Speakers are asked to use the preview room prior to the opening of their session to prepare their slides for presentation.

Accreditation

The Southern Thoracic Surgical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. One credit hour in category I of the Physician's Recognition Award of the American Medical Association may be claimed for each hour of participation by the individual physician.

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Ann Thorac Surg 1989;48:458–62 • 0003-4975/89/$3.50

PROGRAM
FOR THE THIRTY-SIXTH ANNUAL MEETING OF THE SOUTHERN THORACIC SURGICAL ASSOCIATION

November 9–11, 1989
The Phoenician Resort, Scottsdale, AZ

November 9, 1989 (Thursday)
Postgraduate Program

7:45 Introduction to the 1989 Postgraduate Course
Course Director: Andrew S. Wechsler, Richmond, VA

Questions and answers will follow each presentation.

Cardiac Infections

7:50 Acute Valvar Endocarditis (Antibiotic Management, Operative Timing, Special Diagnostics)
Robert A. Guyton, Atlanta, GA

8:10 Mitral Valve Endocarditis (Operative Management, Native vs Prosthetic)
Meredith L. Scott, Orlando, FL

8:30 Aortic Valve Endocarditis
Gulshan K. Sethi, Tucson, AZ

8:50 Fungal Endocarditis
Irving L. Kron, Charlottesville, VA

9:10 Mediastinal Infection
Joseph M. Craver, Atlanta, GA

9:30 Break
Visit Exhibits

Lung Cancer

10:15 Diagnosis and Staging
James W. Brooks, Richmond, VA

10:35 Bronchoplasty, Segmentectomy, Wedge Resection
Kamal A. Mansour, Atlanta, GA

10:55 Pre-Op Radiation, Chemotherapy, Complications of Resection
William F. Sasser, St. Louis, MO

11:15 Management and Evaluation of Pulmonary Metastases
E. Carmack Holmes, Los Angeles, CA

Congenital Case

11:35 Defects in the Cardiac Septa
Benson R. Wilcox, Chapel Hill, NC

12:00 Adjourn

November 9, 1989 (Thursday)
First Scientific Session

1:30 1. The Role of Lung Decortication in Symptomatic Pediatric Empyemas
Robert A. Gustafson, Gordon F. Murray, Herbert E. Warden, and Ronald C. Hill, Morgantown, WV

2. Thoracoplasty: Current Application to the Infected Pleural Space
Terrence P. Horrigan and Norman Snow, Cleveland, OH

3. Thoracoscopy and Talc Pleurodesis for Effusions and Pneumothoraces
Thomas M. Daniel, Curtis G. Tribble, and Bradley M. Rodgers, Charlottesville, VA

4. Histoplasmosis Titre and Keticonazole: Critical Adjuncts to Successful Surgical Management of Sclerosing Mediastinitis
H. C. Urschel, M. A. Razzuk, and S. Y. Chung, Dallas, TX

2:45 Break
Visit Exhibits

3:30 Presidential Address
Richard E. Clark, Bethesda, MD

4:15 **Surgical Forum**

5. Normalization of Postischemic Calcium Levels Improves Ventricular Performance Without Adverse Effects on Compliance and Oxygen Demands
Hideo Yokoyama, Jakob Vinten-Johansen, J. Steve Julian, William E. Johnston, Tonya D. Smith, and A. Robert Cordell, Winston-Salem, NC

6. Oxygen Free Radical Scavengers Decrease Reperfusion Injury in Lung Transplantation
Frank C. Detterbeck, Eric Kron, Douglas E. Paull, Blair A. Keagy, and Benson R. Wilcox, Chapel Hill, NC

7. Leukocyte Depletion Provides Excellent Protection of Heart-Lung Function Following 12 Hours of Static Cold Storage
Ravi Pillai, Ko Bando, Stephan Schueler, Melissa Zebley, Bruce A. Reitz, and William A. Baumgartner, Baltimore, MD

8. 16,16 Dimethyl Prostaglandin E2 Inhibits In Vitro and In Vivo Lymphocyte Responses in Solid Organ Transplantation
Christopher D. Stone, Bruce R. Rosengard, Robert C. Robbins, Hani A. Hennein, David H. Sachs, and Richard E. Clark, Bethesda, MD

9. Cardioplegic Protection for Transplantation: Failure of an Extracellular Solution Compared to Stanford or University of Wisconsin Solutions
John Parker Gott, Pan-Chih, Lynne M. A. Dorsey, Edson H. Cheung, Charles R. Hatcher, Jr, and Robert A. Guyton, Atlanta, GA

10. Superior Preservation With UW Solution After Prolonged Ischemia in the Rat Heart
Thomas Yeh, Jr, Scott A. Hanan, Danna E. Johnson, Ivan M. Rebeyka, Anwar S. Abd-Elfattah, K. Francis Lee, Gert E. Tuchy, Marcos R. Borges, and Andrew S. Wechsler, Richmond, VA

11. The Inhibition of Endothelial Cell Produced Thromboxane by a Calcium Channel Blocker
Fuad Ramadan, Gilbert Upchurch, Blair Keagy, and George Johnson, Jr., Chapel Hill, NC

5:30 Thursday Session adjourned

November 10, 1989 (Friday)
Second Scientific Session

8:00 12. Results of Homograft Replacement for Active Aortic Valve Endocarditis
Ishik C. Tuna, Thomas A. Orszulak, Hartzell V. Schaff, and Gordon K. Danielson, Rochester, MN

13. Management of Postoperative Thoracic Aortic and Periaortic Infections
Joseph S. Coselli and E. Stanley Crawford, Houston, TX

14. Risk of Intervention Following Coarctation Repair
Irving Kron, Terry Flanagan, Karen Rheuban, Howard Gutgesell, and Stanton Nolan, Charlottesville, VA

15. Management of Patients With Thoracic Ectopic ACTH Syndrome
Harvey Pass, Mark Stovroff, John Vetto, John Doppman, Lynnette Nieman, and Gordon Cutler, Bethesda, MD

16. Neodynium YAG Laser and Brachytherapy in the Management of Inoperable Bronchogenic Carcinoma
Joseph I. Miller and Thomas R. Phillips, Atlanta, GA

9:15 Break
Visit Exhibits

November 10, 1989 (Friday)
Third Scientific Session

10:00 17. Cardiac Tumors: Clinical Spectra, Diagnoses, and Changing Management from a 25-Year Experience
Michael C. Murphy, Michael S. Sweeney, J. B. Putnam, Jr, William E. Walker, O. Howard Frazier, David A. Ott, and Denton A. Cooley, Houston, TX

18. Outcome of Heart Transplant Candidates Without Transplantation: The Current Era (1983–1989)
Duke E. Cameron, Peter S. Greene, Stephen C. Achuff, Alfred S. Casale, Timothy J. Gardner, Sharon M. Augustine, Bruce A. Reitz, William A. Baumgartner, Baltimore, MD

19. The Use of Potentially Infected Donor Hearts for Cardiac Transplantation
David E. Lammermeier, Michael S. Sweeney, Hans E. Haupt, J. Michael Duncan, and O. Howard Frazier, Houston, TX

11:00 Guest Speaker
Research and the Practicing Surgeon
Mark V. Braimbridge, London, England

11:30 Business Meeting (members only)

12:30 Friday Session adjourned

November 11, 1989 (Saturday)
Fourth Scientific Meeting

8:00 20. Surgery for High Cervical Esophageal Carcinoma: Experience With Twelve Patients
Kamal Mansour, Anthony Picone, and John Coleman, Atlanta, GA

21. Esophageal Perforation—A Therapeutic Challenge
Safuh Attar, John R. Hankins, Thomas R. Coughlin, and Joseph S. McLaughlin, Baltimore, MD

22. True Emergency Coronary Bypass Surgery
Fred H. Edwards, Amram Cohen, LeNardo Thompson, Ronald Bellamy, and Michael Barry, Washington, DC

23. Surgical Back-up of Percutaneous Transluminal Coronary Angioplasty (PTCA): Results of a National Survey to Determine Patterns of Practice
Duke E. Cameron, Dean C. Stinson, Peter S. Greene, and Timothy J. Gardner, Baltimore, MD

24. Reoperation in the ICU Setting
George Kaiser, Keith Naunheim, Andrew Fiore, Howard Harris, Lawrence McBride, D. Glenn Pennington, Hendrick Barner, and Valle Willman, St. Louis, MO

25. Four Years Experience With Fibrin Sealant in Thoracic and Cardiovascular Surgery
T. L. Matthew, W. D. Spotnitz, I. L. Kron, T. M. Daniel, C. G. Tribble, and S. P. Nolan, Charlottesville, VA

9:45 Break
Visit Exhibits

November 11, 1989 (Saturday)
Fifth Scientific Session

10:30 26. Selective Monitoring of Patients With Suspected Blunt Cardiac Injury
James Reif, J. Justice, W. R. Olsen, and Richard L. Prager, Ann Arbor, MI

27. Predicted Postoperative Pulmonary Function Correlates With Operative Mortality and Long-Term Survival Following Pneumonectomy in Patients With Primary Lung Carcinoma
David E. Lammermeier, J. B. Putnam, Jr, Marion J. McMurtrey, and Jack A. Roth, Houston, TX

28. Repair of Supravalvar Aortic Stenosis: Hemodynamic Results and Coronary Artery Size
Paul W. Braunstein, Paul C. Oslizlok, Fred A. Crawford, and Robert M. Sade, Charleston, SC

29. Reappraisal of Localized Resection for Subvalvular Aortic Stenosis
James R. Stewart, Walter H. Merrill, John W. Hammon, Jr, Thomas P. Graham, and Harvey W. Bender, Jr, Nashville, TN

30. Facile Retrograde Cardioplegia: Report of 225 Consecutive Cases Using Transatrial Cannulation of the Coronary Sinus
Steven R. Gundry, Alexandro Sequiera, Joseph McLaughlin, and Leonard L. Bailey, Loma Linda, CA, and Baltimore, MD

31. Valvular Insufficiencey After Ultrasonic Debridement for Aortic Stenosis
Joseph M. Craver, Atlanta, GA

12:30 Annual Meeting ends

THE ANNALS OF THORACIC SURGERY
Official Journal of The Society of Thoracic Surgeons and the Southern Thoracic Surgical Association

EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information.

Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

Thirty-eighth Annual Meeting of The Scandanavian Association for Thoracic and Cardiovascular Surgery and The Scandanavian Society for Extracorporeal Technology, Aarhus, Denmark—September 13–16, 1989

For information on this meeting, contact the Secretary of the Congress Committee SATCVS/SCANSECT, Chr. Mouritzen, MD, Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus-Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

Third Annual Meeting of the European Association for Cardio-Thoracic Surgery, Munich, Federal Republic of Germany—October 9–11, 1989

For information on this meeting, contact Organizing Secretariat, Interplan Convention and Visitor Service, Sophienstrasse 1, D-8000 Munich 2, FRG; or telephone 089 59 44 92 (telex: 523183 iplan d; facsimile: 089 59 16 10).

Sixth World Congress of Bronchoesophagology, Tokyo, Japan—October 15–18, 1989

This meeting is sponsored by the Organizing Committee of the Sixth World Congress of Bronchoesophagology, the Japan Broncho-esophagological Society, and the Foundation for Advancement of International Science under the auspices of the International Bronchoesophagological Society. For information, contact the Secretariat of the Sixth World Congress of Bronchoesophagology, c/o Japan Convention Services, Inc, Press Center Bldg, 2-2-1 Uchisaiwaicho, Chiyoda-ku, Tokyo 100, Japan; or telephone 03-508-1213 (telex: J33104; facsimile: 03-508-0820).

American College of Surgeons, Atlanta, Georgia—October 15–20, 1989

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050.

Sixteenth World Congress on Diseases of the Chest and the Fifty-fifth Annual Scientific Assembly, American College of Chest Physicians, Boston, Massachusetts—October 30–November 3, 1989

This meeting is sponsored by the American College of Chest Physicians and the International Academy of Chest Physicians and Surgeons. For information, contact the American College of Chest Physicians, 911 Busse Highway, Park Ridge, IL 60068; or telephone (312) 698-2200.

Thirty-sixth Annual Meeting of the Southern Thoracic Surgical Association, Scottsdale, Arizona—November 9–11, 1989

For information on this meeting, contact Gordon F. Murray, MD, Southern Thoracic Surgical Association, 111 East Wacker Dr, Chicago, IL 60601-4301; or telephone (312) 644-6610.

Sixty-second Scientific Session of the American Heart Association, New Orleans, Louisiana—November 13–16, 1989

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 750-5300.

Twenty-fifth Anniversary—Open Heart Surgery, Jerusalem, Israel—December 28, 1989–January 1, 1990

For information on this meeting, contact Joseph B. Borman, MD, or the Secretariat, PO Box 32390, Jerusalem 91323, Israel; or telephone 972-2-663171 (telex: 26205 TRGBL IL; facsimile: 972-2-665277).

Specialty Review in Thoracic Surgery, Chicago, Illinois—January 8–13, 1990

This course is sponsored by the Cook County Graduate School of Medicine and is accredited for approximately 47 hours in category 1 of the Physician's Recognition Award of the AMA. For information, contact the Registrar's office: within Illinois, 1 (800) 621-4649; outside Illinois, 1 (800) 621-4651.

New Trends in Aortic Valve Surgery (Auto, Allo, Xenografts and Reconstruction), Riyadh, Saudi Arabia—January 17–18, 1990

For information on this workshop, contact Department of Cardiovascular Diseases, King Faisal Specialist Hospital & Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia (facsimile: 966-1-441-4839).

Esophageal Disorders: Pathophysiology and Treatment, Maui, Hawaii—January 25–30, 1990

This program is sponsored in part by educational grants from Synectics Medical, Inc, and Smith Kline & French Laboratories, and is accredited for 24 hours in category 1 of the Physicians Recognition Award of the AMA. For information on this meeting, contact Department of Surgery, Creighton University, CME Program, 601 North 30th St, Omaha, NE 68131; or telephone (402) 280-4501 (facsimile: (402) 280-4593).

Twenty-seventh Annual Seminar—Coronary Atherosclerosis: New Diagnostic and Therapeutic Approaches, Orlando, Florida—January 28–February 1, 1990.

This seminar is sponsored by the Departments of Radiology and Cardiology, Mount Sinai Medical Center of Greater Miami, Miami Beach, FL, and is accredited for 20.5 hours in category 1 of the Physician's Recognition Award of the AMA. For information on this meeting, contact Lucy R. Kelley, Program Coordinator, Radiology Seminars, Inc, PO Box 143762, Coral Gables, FL 33114-3762; or telephone (305) 674-2810.

Nineteenth Annual Meeting of the German Society for Thoracic, Cardiac, and Vascular Surgery, Bad Nauheim, Federal Republic of Germany—February 22–24, 1990

For information on this meeting, contact Hagen D. Schulte, MD, Professor of Surgery, Department of Thoracic and Cardiovascular Surgery, Heinrich-Heine-University, Moorenstrasse 5, D-4000 Dusseldorf, Federal Republic of Germany.

Thirty-ninth Annual Meeting of the American College of Cardiology, New Orleans, Louisiana—March 18–22, 1990

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone 1 (800) 253-4636.

Aortic Surgery Symposium II, New York, New York—May 4–5, 1990

This symposium is sponsored by Meadox Medicals, Inc, and is accredited for 15 hours in category 1 of the Physician's Recognition Award of the AMA and toward the New York Medical Association Certificate in Continuing Medical Education. For information, contact Beverly Farrier, Symposium Coordinator, ProMedica International, 620 Newport Center Drive, Suite 575, Newport Beach, CA 92660.

Seventh Congress of the European Society of Biomechanics, Aarhus, Denmark—July 8–11, 1990

For information on this meeting, contact Seventh Congress of ESB, Biomechanics Laboratory, Orthopaedic Hospital, Randersvej 1, 8200 Aarhus N, Denmark; or telephone 45-616-7500, extension 4649.

CLASSIFIED ADS

Classified ads for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Media for Medicine, Inc, 440 Park Avenue South, New York, NY 10016 (telephone: (212) 684-5540; facsimile: (212) 545-0651). All ads are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **$1.10 per word per insertion, minimum 20 words.** Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of $15.00 per insertion for box number ads.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Ad orders should be for a maximum of 6 months; ads may be renewed for up to 6 months at a time. Ad copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Ads, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3695). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

Please note that *The Annals* does not function as a placement service and cannot provide information on advertised positions. When answering advertisements, please write individually to each advertiser you wish to contact, using the address given in the ad. To respond to an anonymous ad, write to Box Number, *The Annals of Thoracic Surgery*, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010.

SITUATIONS AVAILABLE

Cardiothoracic surgeon needed for rapidly expanding program located in a coastal area of the Southeast. Private practice, primarily adult cardiac and thoracic. BC/BE required. Respond with curriculum vitae and names of references.

Please respond to Box 102. 102G/C

Cardiothoracic surgeon, board certified with 2 to 4 years experience in cardiac surgery, wanted to join a growing group of cardiac surgeons, cardiologists, and pulmonologists in the Pacific Northwest. General thoracic and vascular experience necessary. Research opportunities available, academic links possible. Salary leading to full partnership in 2 or 3 years; potential exists for leadership in major cardiac program.

Please send curriculum vitae to John R. Bauman, Administrator at The Thoracic Clinic, PC, 507 NE 47th Ave, Portland, OR 97213-2282. 124C/I

Cardiothoracic and vascular surgeon, board eligible/certified with experience in adult cardiac thoracic and vascular surgery, wanted to join well established 2-surgeon practice located in South Florida. Send CV.

Please respond to Box 105. 105C/B

Cardiothoracic surgeon to join established group in northwest Indiana (very near Chicago). Excellent salary. Please respond with curriculum vitae.

Please respond to Box 104. 104I/L

Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible cardiovascular and thoracic surgeon to join a large cardiac surgery group in southern California. Must have a minimum of 1 year experience in pediatric and neonate cardiac surgery (including fellowship). Excellent fringe benefits. Respond with curriculum vitae.

Please respond to Box 144. 144E/D

Cardiothoracic surgeon: Board certified or eligible is sought to join an academic practice in the Midwest. Opportunity to become active and contribute to a growing cardiothoracic transplantation program. Excellent research opportunities available.

Direct curriculum vitae or inquiries to J. Terrance Davis, MD, Medical College of Ohio, C.S. #10008, Toledo, OH 43699. An equal opportunity employer. 153F/I

Cardiothoracic/vascular surgeon wanted to join established practice in Ohio. Recent graduate preferred. Please submit curriculum vitae and three references.

Please respond to Box 172. 172G/K

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Please respond to Box 174. 174G/I

Thoracic surgeon: Board certified or eligible. Interested in practice of thoracic, vascular, and general surgery in the greater Cincinnati area. Send resume.

Please respond to Box 170. 170G/I

Cardiovascular and thoracic surgeon, board eligible or certified, to join expanding practice in Rocky Mountain region. Salary leading to full partnership. Please send CV and references.

Please respond to Box 165. 165G/J

Thoracic and cardiovascular surgeon, board certified or eligible, wanted for an established practice in the Midwest with experience in adult cardiac, thoracic, and peripheral vascular surgery. Experience or training in heart/lung transplantation preferred. Initial contact should include curriculum vitae, clinical experience, and names of references.

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Additional cardiothoracic surgeon, BC/BE, to join expanding practice of cardiac/thoracic surgery at 500-bed affiliate of major medical center in Midwest. Skills in internal mammary grafting, valve repair, ventricular assist important, and familiarity with electrophysiological procedures desired. Excellent investigational facilities available with ample opportunity for clinical or basic science research. Private practice with academic affiliation—solid general surgery residency with active medical student participation. Salaried position leading to eventual partnership for the right individual. Send CV.

Please respond to Box 178. 178G/I

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Please respond to Box 180. 180HI

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Please respond with curriculum vitae outlining training and recent surgical experience to Virginia Heart Surgery Associates, 3301 Woodburn Road, Suite 301, Annandale, VA 22003. 183H/J

Cardiothoracic surgeon: Private practice position, Great Lakes, adult cardiothoracic and vascular surgery. Must be currently active in cardiac surgery. Send CV and references.

Please respond to Box 184. 184HI

Cardiovascular/thoracic surgeon, BC/BE, needed to join busy expanding private practice in Colorado Springs. Adult and pediatric cardiothoracic and some vascular. Initial contact should include curriculum vitae and references.

Please send CV and three reference letters to E. S. Yee, MD, Director of Cardiovascular Surgery, 1725 E Boulder St, Suite 104, Colorado Springs, CO 80909. 185H/J

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Please respond to Box 195. 195I/K

Thoracic/vascular surgeon, boarded, preferably with vascular certificate, wanted to join established practice in Southeast. Cardiac capability available. Immediate opening. Please respond with curriculum vitae.

Please respond to Box 196. 196I

Cardiovascular and thoracic surgeon, BE/BC, to join established private practice in San Francisco Bay area. Practice includes adult cardiac, thoracic, and vascular surgery. Initial contact should include curriculum vitae and references.

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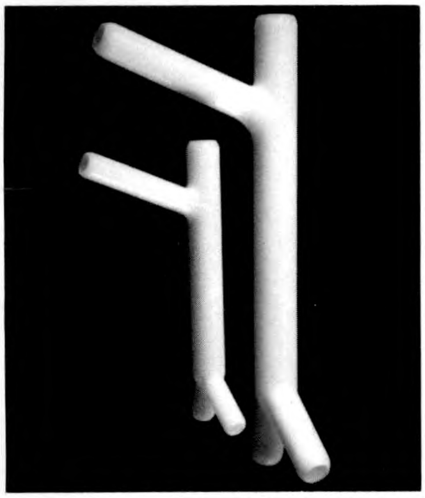

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Westaby, S., Jackson, J. W., and Pearson, F.G. A bifurcated silicone rubber stent for relief of tracheobronchial obstruction. *J. Thorac. Cardiovasc. Surg.* 83:414, 1982.

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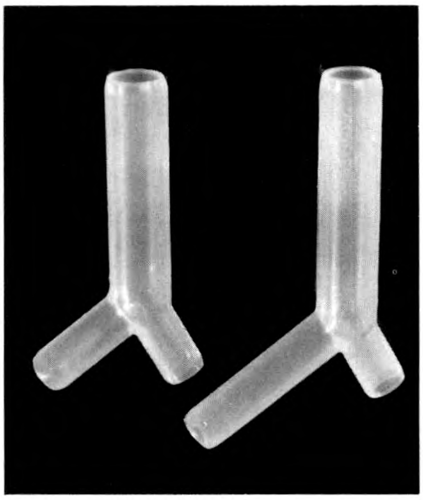

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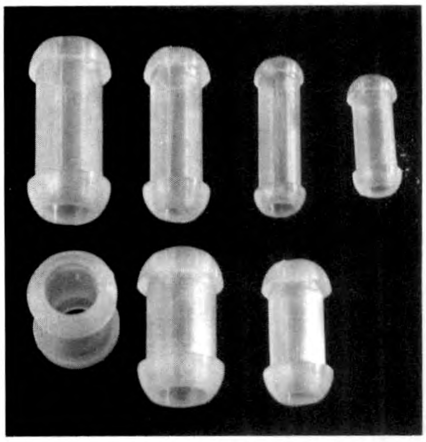

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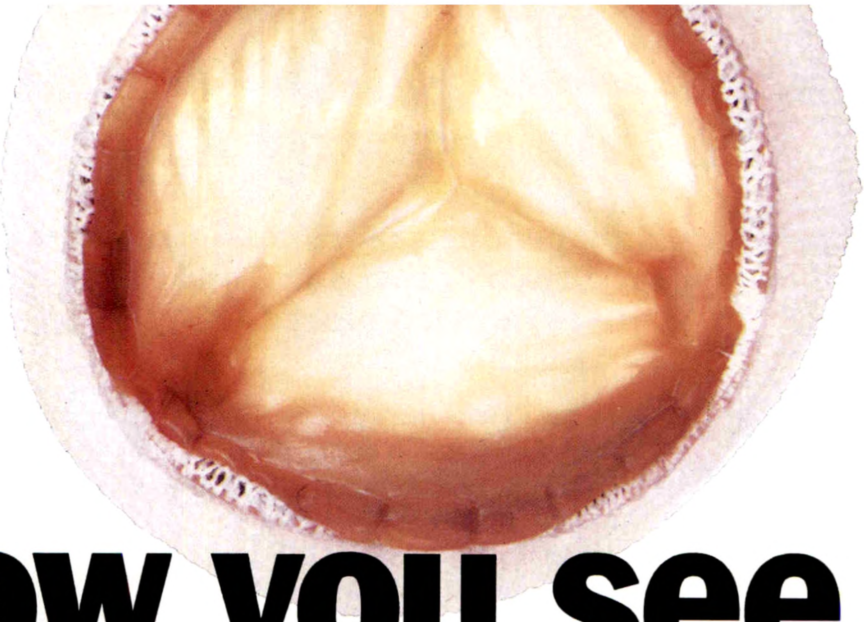

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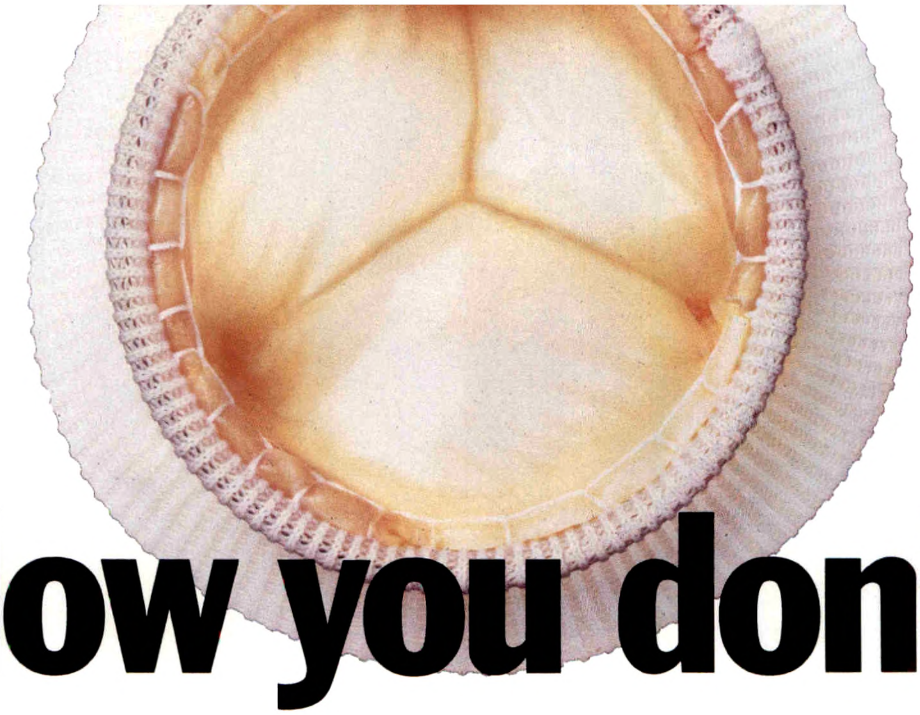

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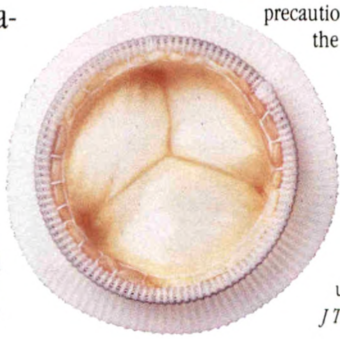

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1. DiSesa VJ, Allred EN, Kowalker W, et al: Performance of a fabricated trileaflet porcine bioprosthesis: Midterm follow-up of the Hancock modified-orifice valve. *J Thorac Cardiovasc Surg* 1987;94:220-224.

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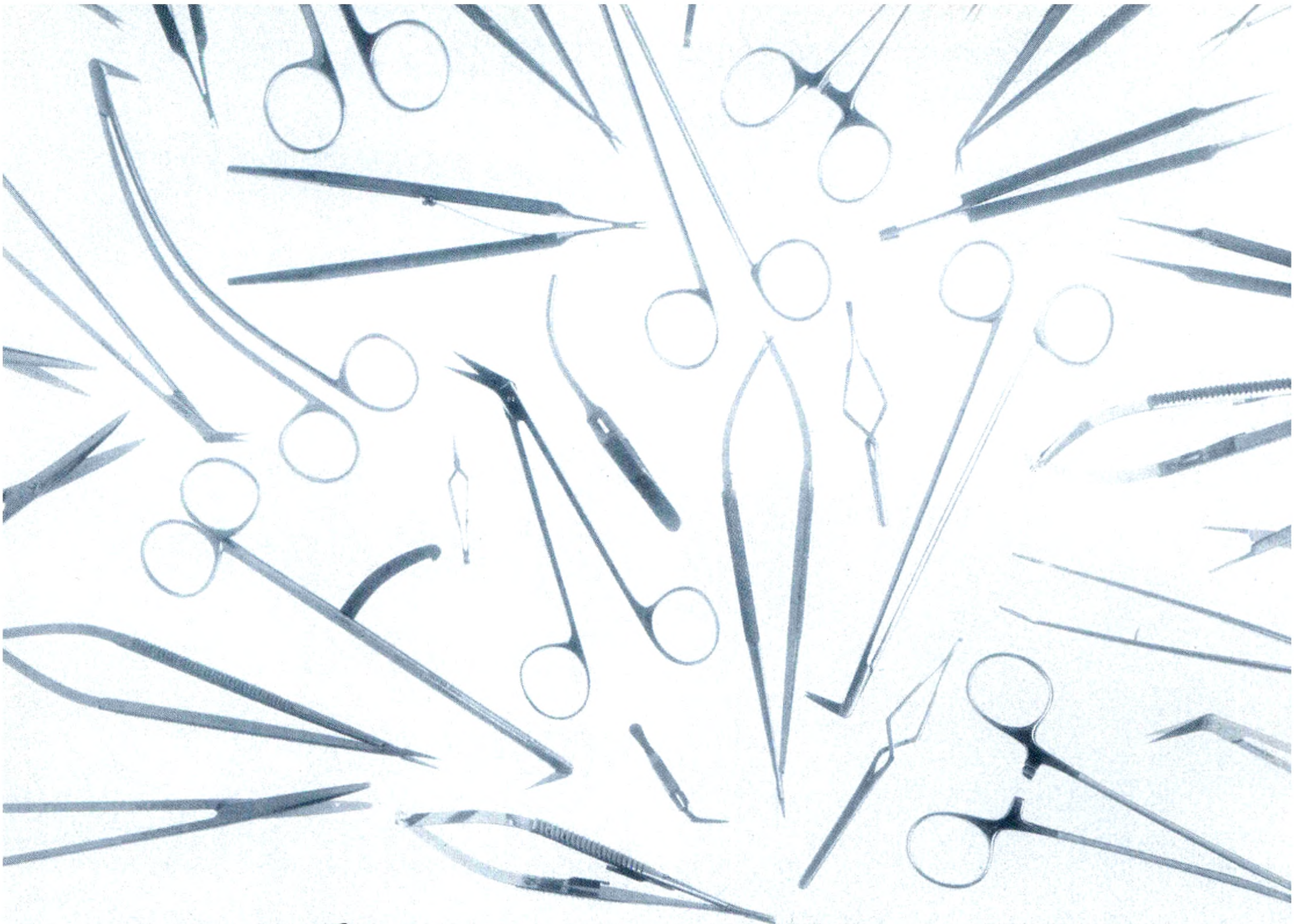

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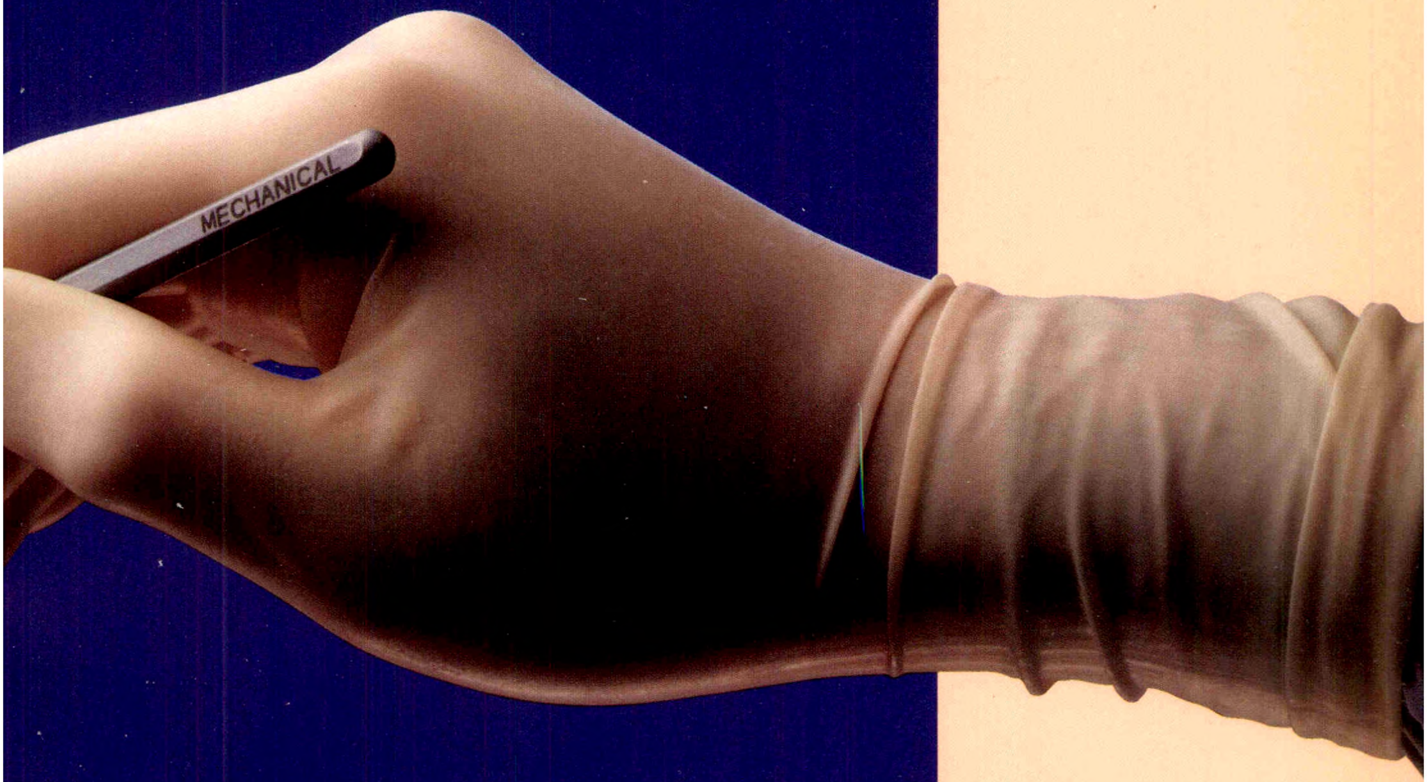

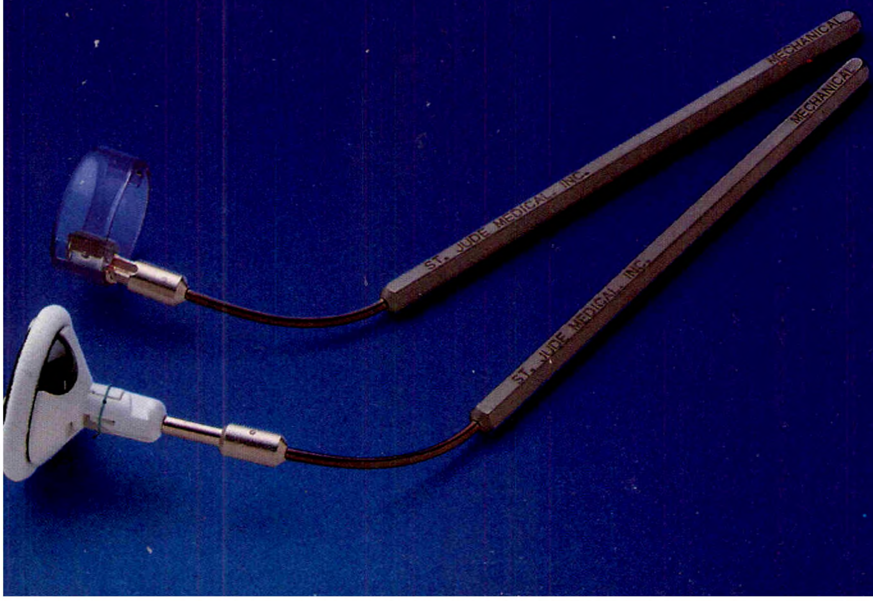

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SUPPLEMENT TO THE ANNALS OF THORACIC SURGERY

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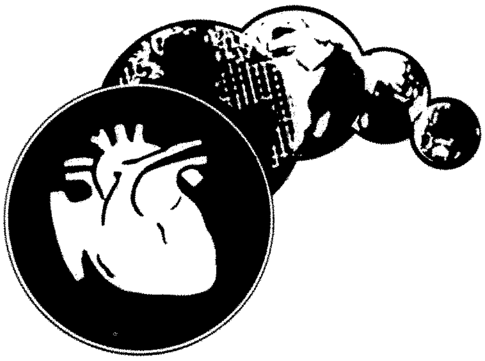

Arthur C. Beall, Jr, MD
Guest Editor

January 15-18, 1989
Hotel del Coronado
San Diego, California

Even though beginning in 1953 cardiopulmonary bypass permitted direct vision of cardiac valves, effective therapy for most patients with acquired valvular heart disease was still not possible because of the advanced disease state of the valve. Just over a quarter of a century ago prosthetic heart valves became available. Many problems were associated with these early models, but to paraphrase Dwight Harken, they were safer than the diseases that they were used to treat. Since then many modifications have been made in cardiac valve prostheses, and most have resulted in substantial advances. Some, unfortunately, created more problems than improvements. Allograft valves were introduced, and numerous tissue prostheses were constructed, along with ingenious methods of preservation. In spite of the pitfalls, progress has been sustained.

Almost all of the pioneers in this quarter century of innovation still are alive, and January 1989 seemed an auspicious time to invite them to gather for reunion and reflection. San Diego, California, was selected for the meeting site, and the Hotel del Coronado served as a gracious host. Many companies in the heart valve and suture fields were generous in helping defray the expenses of the meeting and of this publication.

As a reunion and social gathering, the Congress proved an outstanding success. So too were the presentations. Many pioneers who spoke are no longer involved in the valve field, and others long since have retired. Nevertheless, physicians, engineers, other scientists, and manufacturers enjoyed recalling their collaborations, as well as their disagreements. Some personal experiences were related that previously had not found their way into print. Several long-term follow-ups were presented, and methods of statistical analyses were discussed. Finally, a few speakers chanced a look into the future of heart valve replacement.

The Editor of *The Annals*, Dr Tom Ferguson, and his Administrative Editor, Carol Blasberg, have been most helpful in putting together the material submitted by the speakers. Hopefully, we have recorded how the heart valve field arrived at where it is today. However, unless we hark the words of Larry Pilot in his article, we may never again see such rapid strides in improving the care for these patients.

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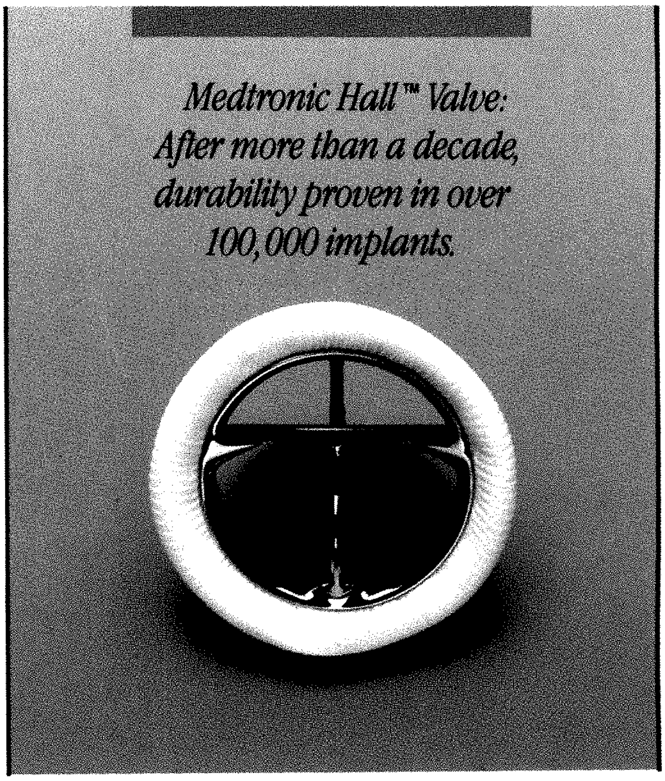
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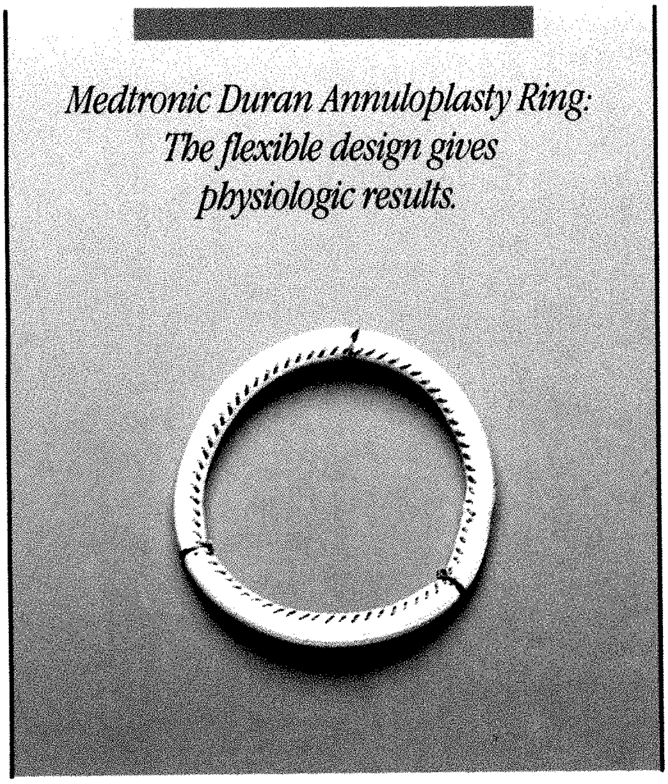
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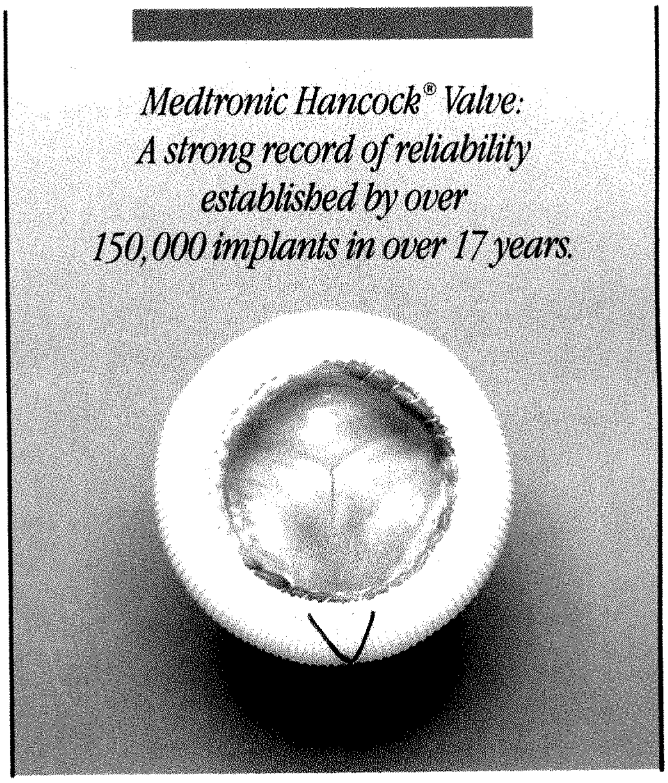
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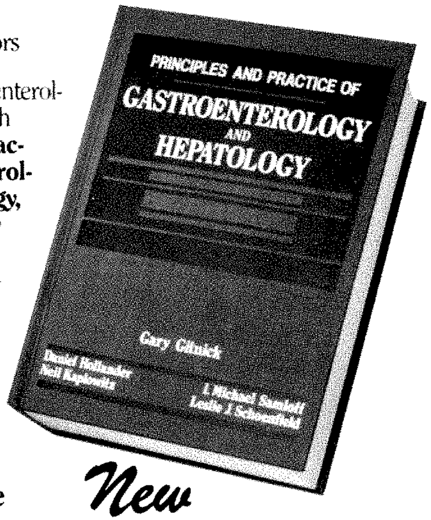

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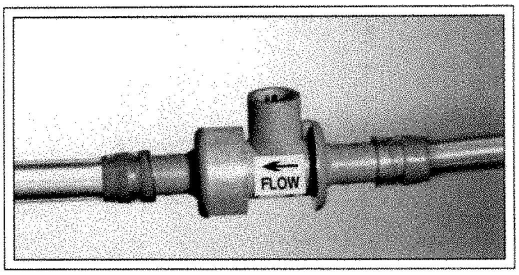

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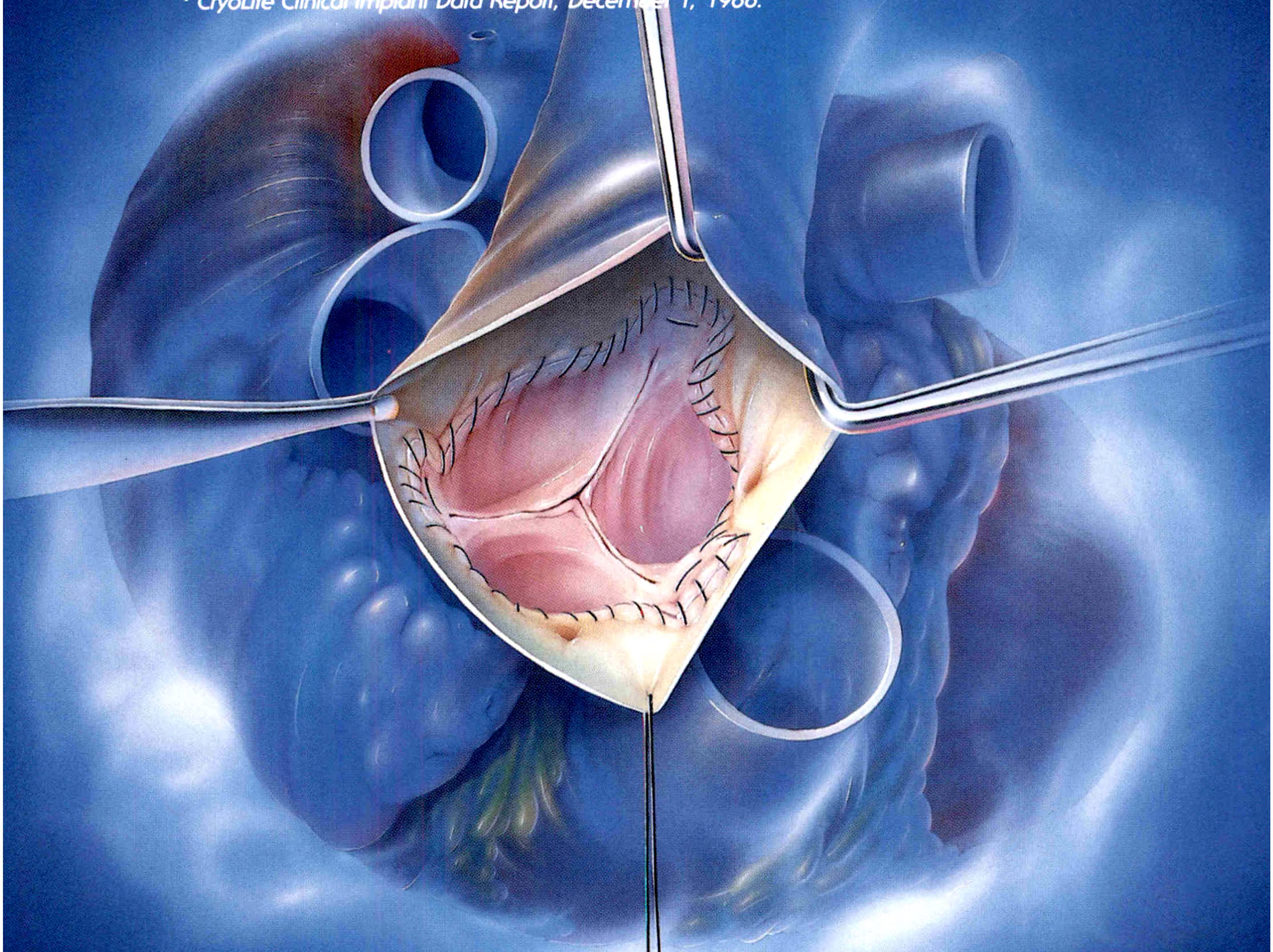

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It Will Work: The First Successful Mitral Valve Replacement

Nina S. Braunwald, MD

Division of Cardiac Surgery, Brigham and Women's Hospital, Boston, Massachusetts

In 1959, a prosthetic mitral valve of flexible polyurethane with Teflon chordae tendineae was designed and fabricated. After a series of experiments in dogs carried out at the Clinic of Surgery at the National Heart Institute, on March 11, 1960, this valve was used as a total replacement of the mitral valve of a 44-year-old woman with mitral regurgitation. After an uneventful postoperative course, she was discharged from the hospital and did well thereafter, but died suddenly, presumably of an arrhythmia, 4 months after operation.

(Ann Thorac Surg 1989;48:S1–3)

The environment in which we train and the scientific problems of the time help to shape the course of the kind of research problems that we tackle. I completed my residency training in General Surgery as Chief Resident at Georgetown University Medical Center at a time when Charles Hufnagel, newly arrived from Boston, was using a methyl methacrylate ball valve prosthesis in the descending aorta for the treatment of aortic regurgitation. Armed with a core knowledge of biomaterials and heart valve modifications and graduate training in tissue transplantation, I was offered and accepted a staff position and my own laboratory in the Clinic of Surgery of the intramural program of what was then the National Heart Institute.

Together with another then-young investigator, Theodore Cooper, later Assistant Secretary of Health and now Chief Executive Officer of Upjohn, I began laboratory investigations on the development of a prosthesis that would completely replace the mitral valve at a time when patients with end-stage mitral regurgitation were dying regularly despite vigorous medical treatment.

Material and Methods

Using hearts from animals and humans, plaster casts were made of normal mitral valves, the annulus, and the tissue around the atrioventricular junction. Using a plastic steel called Devcon, two-piece molds from which the finished valves were to be fabricated were made. A thin Dacron locked knit fabric was stretched over the male half of the mold and cemented in place, and the female half of the mold was filled with an open cell liquid polyurethane [1]. The mold was closed while the polymer was setting to assure that the leaflets would remain thin. Woven Teflon fabric chordae tendineae, made specially for us by the U.S. Catheter Co, were sewn to the valve leaflets (Fig 1).

During the developmental phase of the work, valve function was tested in the laboratory using a pulse duplicator modeled on the one described by Davila and colleagues [2]. The fabricated valve was sewn into hearts obtained at autopsy. This permitted leaflet motion to be correlated with atrioventricular distention at various pulse rates and left atrial pressures. It soon became evident that the length of the artificial chordae was crucial in assuring valve competency with a prosthesis in which the leaflets were extremely pliable. If the chordae were too tight, the valve was rendered incompetent in the open position; if they were too loose, the leaflets prolapsed into the left atrium, again causing incompetence.

Once fabricated, the prosthesis was used to replace the mitral valve in 24 dogs with the aid of cardiopulmonary bypass, a technique that had been introduced into cardiac surgery a relatively short time previously. The left atrial pressure could be altered by adjusting the length of the artificial chordae. In surviving dogs, the left atrial pressure was found to be in the normal range. At the time of postmortem examination, a thin platelet fibrin deposit was seen covering the leaflets. After review of the progress in the laboratory, the decision was made to employ this valve in a patient with end-stage mitral regurgitation in whom a reconstructive procedure was not possible [3–5].

On March 11, 1960, with Dr Morrow at the table, I completely replaced the diseased mitral valve of a 44-year-old woman with the flexible open cell prosthetic mitral valve described.

The patient had had a heart murmur of mitral regurgitation since the age of 8 years and was in New York Heart Association functional class IV with severe congestive heart failure despite intensive medical management. Her valve was noted to be severely thickened and scarred; the left atrium and ventricle were huge. The prosthetic valves had been fabricated in several annulus sizes and an appropriate one was sewn into the mitral annulus using four equidistant tacking sutures; the suture line was completed with a running suture. The artificial chordae had been brought out of the left ventricular wall in the region of the papillary muscle through small stab wounds. After ending bypass and allowing the left ven-

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Presented at the World Congress on Heart Valve Replacement, San Diego, CA, Jan 15–18, 1989.

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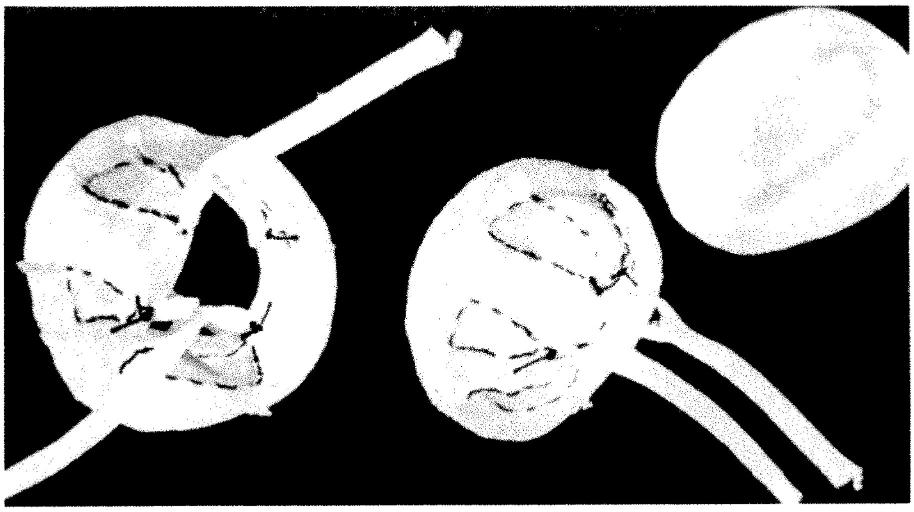


Fig 1. The completed valve after attachment of the chordae tendineae. (Reproduced from [3] by permission of The C.V. Mosby Company.)

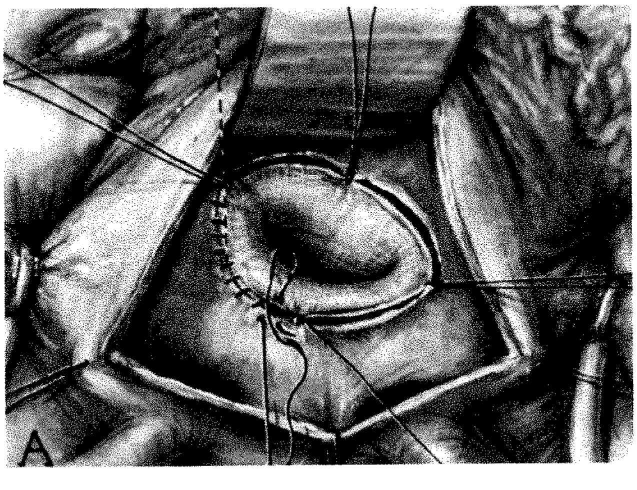
tricle to assume its normal dimensions and contractility, these chordae were fixed in place with Teflon felt pledgets (Fig 2). The leaflets were then fixed to the ventricular wall in diastole over Teflon felt pledgets.

After the patient was weaned from cardiopulmonary bypass, the left atrial pressure was in the normal range, confirming satisfactory valve function. A small diastolic pressure gradient across the prosthetic valve was noted at the conclusion of the procedure.

The patient made an uneventful recovery and was discharged fully ambulatory from the hospital on May 22, 1960, clinically improved. No precordial murmur was audible. Four months after operation, her referring cardiologist called to say that she had experienced arrhythmias and had died one day after being admitted to a local hospital for an arrhythmia. Her heart was returned to the National Institutes of Health for postmortem examination. The leaflets of the prosthesis were thin and pliable, with a thin fibrinous deposit over the polyurethane surfaces. The Teflon pledgets at the site of exit of the chordae tendineae on the ventricle were all well healed.

Comment

During the course of developing an open cell polyurethane leaflet mitral valve, it was appreciated that when the leaflets were made thin and pliable enough to provide minimal resistance to flow they would invert during systole, unless artificial chordae tendinae were used to restrict their motion. Once a technique was developed for optimizing tension on the chords in a beating heart, complete replacement of the mitral valve was achieved in a woman who was discharged from the hospital after an uneventful postoperative course. This was carried out at a



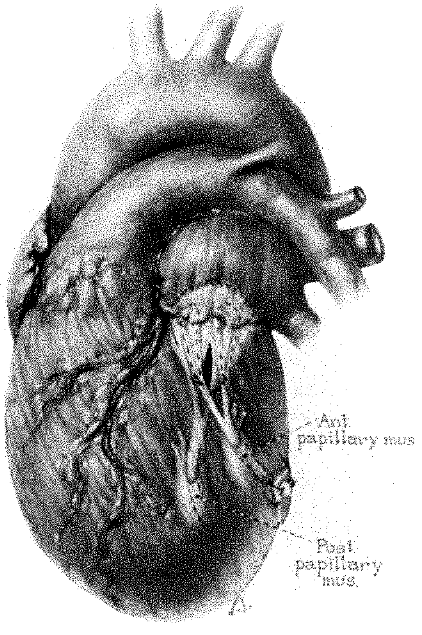


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Fig 2. (A) Fixation of the valve to the mitral annulus; the prosthesis is sutured to the annulus. (B) Appearance of the flexible polyurethane mitral valve prosthesis after insertion and adjustment of the artificial chordae tendineae. Reproduced from [3] by permission of The C.V. Mosby Company.

time in the history of open heart surgery when this operation (complete replacement of the mitral valve) had, to our knowledge, not been previously carried out, although other investigators were working on valve substitutes.

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The Dog as a Model for Evaluating Prosthetic Heart Valves

Richard D. Jones, PhD, Dennis M. Dreher, BS, and Frederick S. Cross, MD, PhD

Division of Surgical Research, Saint Luke's Hospital, Cleveland, Ohio

Our first attempt to investigate valves for cardiac surgery was the construction of valved shunts in 1954 [1]. These shunts allowed us to operate on the proximal great vessels and to simulate experimentally surgical correction of transposition in the dog before the advent of cardiopulmonary bypass. The subsequent development of the rotating disc oxygenator and surgical adjuncts such as the intracardiac suction tip, localized cardiac hypothermia, and a valved ventricular vent were carried out in our laboratory using dogs [2–5]. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prior to and after its publication by the National Institutes of Health in 1963. The evolution of these techniques of cardiopulmonary bypass in our laboratory is unquestionably attributable to the availability and suitability of the dog as a laboratory model for cardiac surgery.

The dog did not seem to be as suitable a model for the development of a prosthetic heart valve, as most investigators found that the prosthesis quickly became covered with pannus and that evaluation of the prosthesis over the long term was not feasible.

As did others, we found that the thrombus that accumulated on the prosthesis generally was infected. Bounos and associates [6] showed that the dog responds to hemorrhagic shock by damaging the bowel mucosa through the action of proteolytic enzymes so that the gut becomes permeable to bacterial products. Starting from this premise, we demonstrated that cardiopulmonary bypass is a sort of shock and that bacteria enter the circulation during this time [7]. If, however, we prevented bowel damage by preoperative dietary reduction of proteolytic enzymes, as Bounous and associates suggested, and sterilized the gut with antibiotics, and if we followed a rigorous prophylactic postoperative antibiotic regimen, we could achieve more than 90% survival for 1 month after prosthetic valve implantation.

We then proceeded, in conjunction with the prophylactic protocol described above, to make an extensive study of the effectiveness of sustained release of antibiotics incorporated in the sewing rim of the prosthesis [8]. We reasoned that a high level of antibiotic leaching from the sewing rim would prevent bacterial seeding of any thrombus on the valve and allow infection-free healing to take place. To fabricate the sustained release system, crystalline gentamicin was milled into silicone rubber in a ratio of 40% gentamicin sulfate (generously supplied by Dr J. Allen Waitz of the Schering Corporation) in 60% silicone rubber. Approximately 1.4 g of the mixture was placed in a mold and cured in an autoclave. The resultant gentamicin-loaded rings were incorporated in the sewing rims of size 65 Cross/Jones disc prostheses and implanted in the mitral valve area, replacing the normal valve. Tracer studies of release of tritium-labeled gentamicin showed peak concentrations of gentamicin in arterial blood to be near 18 μg/mL on days 1 and 2 and to continue at detectable levels of 2 to 3 μg/mL for more than 1 month. At the time of this report [8], excluding 2 animals who did not survive the operation, we had a survival rate of 87% in 26 animals. More than 75% survived over 2 months. There was an overall average 8.6-month survival time, with 10 animals still alive (Table 1).

Our early attempt at repair of heart valves in 1960 consisted of the construction of single cusp replacements for one leaflet of the aortic valve [9, 10]. At that time we pointed out an important aspect of the design of the normal aortic valve that I would like to reiterate here. The unsupported, single aortic valve leaflet under pressure forms a nearly perfect sphere with its sinus of Valsalva. The design feature of critical importance is that the opening of the valve cusp lies above the greatest diameter of the sphere and the lip of the leaflet is on a latitude on the sphere that is smaller in circumference. This factor insures that the cusp inflates as the blood moves back toward the ventricle, closing the valve without prolapse (see Fig 293 in reference [9]). If the base of the sinus distends, or if the lip of the leaflet is damaged to make the cusp opening of equal or greater diameter than that of the sphere, the valve leaflet will prolapse.

We recently inserted in dogs a series of 20 pericardial leaflet valves constructed on a cloth-covered stent using this design principle. We achieved an average survival of 7 months; 3 dogs (18%) survived less than 1 month, 8 (47%) survived 1 to 5 months, 1 (6%) survived 5 to 9 months, and 5 (29%) survived more than 9 months. With

Table 1. Survival Rate in Dogs With Gentamicin Rims

		Survival (mo)[a]			
Group	No.	0–2	2–5	5–9	>9
Control	16	9 (56)	2 (13)	4 (25)	1 (6)
Gentamicin rim	28	7 (25)	2 (7)	13 (46)	6 (21)

[a] Numbers in parentheses are percentages.

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proper control of the bacteremia inherent in the dog, this animal makes a satisfactory model for testing prosthetic heart valves.

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Memoirs of an Early Heart-Valve Engineer

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Heart surgery is an American invention. Many of the close to half a million cardiac surgical procedures performed around the world today involve artificial heart valves that had their commercial origin in southern California's Orange County.

Twenty-five years ago I began a career that was the culmination of my childhood dreams: to be an engineer working with surgeons. As a heart-valve design engineer at Edwards Laboratories I was working on my first heart-valve patent within 4 months.

It was an unforgettable, unbelievable, exciting, exhilarating, and most satisfying era as we worked to establish a brand new field. While others tried to duplicate the natural shape of human heart valves, Lowell Edwards opted for function, with the elegant simplicity of the caged-ball valve. My job was to design a series of valve sizes and sewing rings.

Dr Albert Starr, my mentor, explained that heart valves cannot be equally proportioned as a ratio of diameter to length, much as a man's pants are not proportionally larger as the waist size increases. We had to tread softly and test carefully because we were in uncharted territory. I obtained calf hearts from the slaughterhouse so that I could learn cardiac morphology. I witnessed, photographed, and filmed many open heart operations, and I attended postmortem examinations. One of my most unforgettable experiences was listening with a stethoscope to the chest of a patient who had one of my valves implanted that morning.

Day by day the impossible became reality: we developed new manufacturing techniques, knitting machines, and assembly methods. It is crucial to remember that this was before the age of computers, before man had set foot on the moon, when biomedical engineering was still unheard of! Artificial heart-valve operations were written up in newspapers as the latest "gee-whiz" items.

Early in 1964 I developed a fast-implanting valve based on Dr Arthur Beall's concept that had spring-loaded pins incorporated in the suture ring and held back by a ripcord suture. When the key suture was cut, the 16 pins sank into the aortic tissue to anchor the valve in place. A photographer was supposed to take pictures during the first animal implantation, but he was so awestruck at the sight of an open heart that he forgot to load his camera. When Dr Beall signaled him to shoot, the cameraman's mouth dropped open.

A few months later, we tested another quick-implantation valve I had developed in response to the Cromie valve. My design had 12 curved needles at the valve periphery, which described a true arc instead of a sweep. Several dogs lived long term. (One was named George after me. It died 3 years later in a car accident.)

One day Dr George Robinson of Montefiore Hospital in New York called and urgently requested pediatric valves for a 4-year-old patient who had outgrown a previously implanted valve. Within 2 weeks we created a veritable smorgasbord of valve sizes, enabling Dr Robinson to obtain a perfect fit. This case was also written up in several newspapers.

We developed an excellent record-keeping system for training-valve materials, assembly methods, and tracing each valve right to the patient. This system would even stand the scrutiny of today's Food and Drug Administration.

I believe that we made the first pulse duplicators with polarized light to study flow patterns and regurgitation. We built high-speed testers to study durability. During the variant Silastic ball crisis, we performed lipid absorption studies and other experiments from which evolved hollow steel balls and disc valves. I designed 72 different valves and 17 knitting machines to make sewing rings and covers for valve struts.

We were striving for glistening pseudointima to be anchored into the cloth; the shape, material, and structure of the sewing ring seemed to hold the key to success. It was exhilarating because the lead time from concept to product was so short. The FDA was not yet on the horizon.

Jim Bentley, Don Shiley, Warren Hancock, and I worked together. Eventually we all left Edwards Laboratories to start our own companies. It is a fact not widely known that in American companies the inventor-engineer receives one dollar per patent. That is why we decided to start our own companies. For a while I also worked with Warren Hancock on porcine valve developments. (My present company, American Omni Medical, Inc, manufactures disposable anti-air embolism valves.) Today there are over 200 third- and fourth-generation medical-product manufacturing companies in Orange County alone that can trace their managerial pedigree back to the original Edwards Laboratories.

Classical dramas present a problem in the first act, inject complications in the second, and finally resolve them in the third. In our "first act" we could do anything. The entry of the FDA into the medical manufacturing environment in 1976 marked our entry into the second act. The FDA is upon us. As I don't believe that we can legislate morality, I don't believe that the American gov-

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ernment can legislate better products. Our industry is driven by two very powerful forces. First, if the product is of inferior quality or does not work properly, nobody will buy it. Second, the threat of lawsuits compels us to make safe products. The logic of free enterprise dictates that these two forces must be satisfied before the FDA. (It is interesting to note that only about 5% of litigation is due to product malfunction. Ninety-five percent of all lawsuits are the result of intraoperative human error.)

Heart valves have come a long way, but I am proud to say that the Starr-Edwards valve's longevity is still the gold standard against which all others are measured. The basic techniques, materials, and theories of achieving optimal orifice-to-outside diameter ratio are still as valid as they were in the halcyon days. About 20 years ago we had already designed the "ultimate" prosthesis, but we lacked (and still lack) the super-flexible, durable, and biocompatible materials to make the actual valves. This is the area that holds the most promise—the inventing of these materials.

Heart valve surgery has also spawned other inventive products and techniques such as extracorporeal membrane oxygenators, balloon catheters, and coronary artery bypass grafting. Recently I underwent two balloon angioplasties. I felt fully confident (and proud) being treated with instruments in whose development I had had a small part.

There is even a new profession: cardiopulmonary bypass perfusion. Our horizons are widening in an exponential fashion. It will be exciting to see how the third act resolves the problems of our grand play.

The next 25 years will surely bring more exciting techniques and innovations in the treatment of heart disease. I hope that most of us will be able to meet in the year 2014, to discuss 50 years of our progress. It will be an interesting meeting!

The Full-Orifice Concept in Prosthetic Heart Valves

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Stimulated by dissatisfaction with the then available prosthetic heart valves, cooperative valve studies were initiated in the spring of 1963 between the Department of Surgery at the Sutter Memorial Hospital and the Engineering Department at California State University, Sacramento. The studies brought together two cardiothoracic surgeons, Dr Edward A. Smeloff and Dr Robert S. Cartwright, and two professors of mechanical engineering, Dr Trevor B. Davey and Dr Boris Kaufman. The objective of the study was to develop an advanced ball prosthesis with the following characteristics: (1) optimized flow through a maximized orifice area, and elimination of blood stasis and turbulence, (2) reduced bulk, and (3) extended durability.

Before a commitment was made to the ball-in-cage design, a number of alternate configurations were considered including flap valves, cusp valves, and disc valves. A variety of means of affixing the prosthesis to the host tissue annulus were also considered. The preliminary explorations suggested that a ball-in-cage–type valve held the greatest potential for success in achieving the aforementioned objectives. A sequence of designs was then produced based loosely on the PEMCO valve, a titanium orifice-seating open cage prosthesis with a silicone poppet. The orifice to ball diameter ratio for this valve was approximately 0.80. An earlier version of this valve with a closed cage used clinically had developed a streamer thrombus from the cage apex, prompting the change to open cage.

The first modifications proposed for the new valve were the increase in ball to orifice diameter ratio to approximately 0.90 and the use of a small secondary cage to prevent jamming of the ball in the orifice. A logical extension of this principle then led to an orifice to ball diameter ratio of 1.00 (ie, the diameter of the ball and orifice would be equal). Simple calculations revealed that improving the ratio from 0.8 to 1.0 reduces the sphere mass by 50% for a given orifice diameter. However, silicone-rubber molding techniques available at that time could not produce perfectly spherical poppets. Consequently, it was necessary to increase the orifice diameter to just slightly greater than nominal ball diameter to allow for ball manufacturing tolerances.

To assess the potential hemodynamic consequences of these changes by comparing prototypes of the new valve with other available prostheses, a sophisticated pulse duplicator was designed and constructed (Fig 1). The pulse duplicator was unique in that it permitted simultaneous slow-motion photography of aortic and mitral valves. Variables explored included ball travel, impact characteristics, orifice configuration, pressure gradients, regurgitation, stagnation and turbulence, and forward flow as a function of beat rate and pressure.

During these studies it was observed that as a consequence of the clearance between the orifice and the ball, there was a slight regurgitation when the ball was in the closed position, which produced a self-washing action on the valve proximal surfaces. Multiple-seating impact or bouncing was eliminated. It was also observed that by altering ball travel, it was possible to substantially affect forward flow and regurgitation. It was determined that optimal forward flow at lowest gradient occurred when cage length permitted ball travel such that in the full open position an outflow or secondary orifice area was created exactly equal to the primary orifice. These engineering design characteristics were incorporated in the SCDK (Smeloff-Cartwright-Davey-Kaufman) valve. It had a V orifice cross-section, and the ball seated on the tips of the secondary cage. Valve durability was studied in a specially designed accelerated wear tester. A series of the SCDK valves was tested at a rate of 800 cpm for the equivalent of approximately 15 years at physiological rates. No structural failures were observed.

During the evolution of the SCDK design, a number of acute clinical emergencies arose necessitating construction of prototype valves, which were implanted in patients. These clinical prototypes were individually handmade by Anton Nirschl, Chief Technician for the School of Engineering, California State University, Sacramento. Because of concern with the introduction of foreign materials and the potential for faulty welds, monobloc titanium construction was specified. All full-orifice prostheses produced thereafter have been constructed in accordance with this specification.

Successes with these individually handcrafted prostheses stimulated an interest in their availability for use at other heart centers, and led to discussions with Cutter Laboratories (Berkeley, CA) with the objective of regular production and wider distribution. These discussions reached fruition in late 1964 and, under the direction of Paul Kahn, Sam Goodenough was made responsible by Cutter for effecting the transition from prototype to production. Unique methods were introduced to simplify the manufacturing process and reduce cost. For example, an electric discharge machining technique was used to remove excess material and bring the struts closer to final configuration. A machine designed for ultrasonic welding of plastics was modified to shape the distal struts to the

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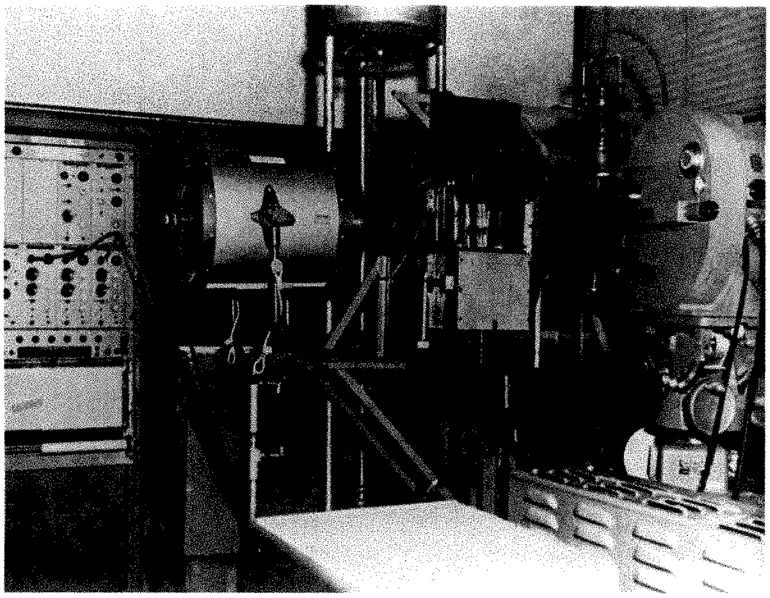

Fig 1. Original pulse duplicator constructed at California State University, Sacramento, for comparative valve study. (Reprinted from Smeloff EA, Huntley AC, Davel TB, Kaufman B, Gerbode F. Comparative study of prosthetic heart valves. J Thorac Cardiovasc Surg 1966;52:841–8, by permission of The C.V. Mosby Co.)

desired curvature. A production staff was trained and quality-control standards established, some of which were ultimately incorporated in the Association for the Advancement of Medical Instrumentation Heart Valve Standards.

The valve, then designated the SCDK-Cutter, was introduced for clinical use both in the US and at foreign heart centers. Ongoing in vitro evaluation of the design suggested that further improvements were possible through modification of the orifice geometry to a radius of curvature, instead of the original V cross section, and also by shaping the proximal cage struts to produce a line rather than a point contact for ball seating. The prosthesis incorporating these modifications was designated the Smeloff-Cutter prosthesis. It was introduced clinically in 1965, and replaced the SCDK-Cutter valve entirely by 1966.

At this time, an industry problem termed "ball variance" arose. Both the SCDK-Cutter and Smeloff-Cutter prostheses were subject to this complication. Studies were initiated in an effort to elucidate and alleviate this problem. They resulted in two changes: (1) modification of the silicone-rubber ball curing process to produce a "mild cure," and (2) modification of the procedures by which the ball was mated to a specific cage. Valves constructed to these specifications were designated as Smeloff-Cutter Present Model valves, and were placed in clinical service in September 1966. This model has not experienced classic ball variance resulting in valve malfunction. The full-orifice concept was subsequently incorporated in other designs such as the Cooley-Cutter valve, initially fabricated with a Pyrolite-carbon lenticular poppet as a mitral prosthesis, which evolved to a prosthesis incorporating a biconical Pyrolite-carbon occluder used for both mitral and aortic positions.

In the Smeloff-Cutter valve consideration was periodically given to substitution of the silicone-rubber poppet by other materials. However, with the mitigation of ball variance in the valves produced after September 1966, the impetus for a materials change diminished. In summary, since their clinical introduction, it is estimated that well over 20,000 full-orifice valves have been implanted worldwide. Clinical experience has been extensively documented. We agree with Starr and colleagues, who concluded that "the Smeloff-Cutter valve is a mechanically reliable and durable prosthesis with proved excellent survival" [1]. In as much as this valve is now in its third decade of continual clinical service without modification, we believe that it has indeed withstood the test of time.

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Reduction of Ball Variance in Silicone Rubber Occluders

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Ball variance was a major cause for concern early in the use of heart valves with silicone rubber occluders [1, 2]. Ball variance can be defined as the physical changes that can occur in vivo accompanying the absorption of simple and complex plasma lipids. The changes are manifested in several ways, including discoloration, weight gain, wear, swelling, and fissuring. Valve function can be compromised by reduced occluder mobility, or by impaction or loss of the occluder.

The SCDK and the Smeloff-Cutter (S-C) valves are double-cage ball valves in which the ball passes through the orifice of the valve, with the equator of the ball essentially occluding the valve orifice. Ball variance is of particular concern because the relationship of the diameter of the ball to that of the orifice must be maintained to assure optimal valve function. Clinical evidence of ball variance was reported in about 2.5% of the SCDK and in about 1% of the early model S-C valves.

Because of the relatively low incidence of variance, we believed that both chemical and physical or environmental factors are involved in the development of ball variance. A major factor appears to be aberrant flow patterns in the prosthesis. Data on early Starr-Edwards valves showed that variance occurred only in the aortic position, where turbulence and impact forces were relatively great, and usually were associated with implantation problems, whereas paired mitral implants showed no variance [2]. On this basis, the problem was approached from several angles.

Development of In Vitro Methods to Duplicate Lipid Pickup and to Evaluate Effect of Silicone Rubber Cure Cycle on Absorption

Variant and nonvariant balls that were returned for examination were analyzed for lipid content [3, 4]. The absorbed material was found to be a mixture of free lipids and relatively polar materials. The free lipids included fatty acid, neutral fat, steroid, steroid ester, and phospholipid; the complex polar materials on analysis were found to consist principally of oxidation products of polyunsaturated fatty acids analogous to linoleic and arachidonic acids. Nonvariant balls had lipid contents up to 1.5%, and variant balls had lipid contents of from 2% to 16%. Simple lipids were absorbed to about 1.5% in variant balls, with the balance being the polar material.

A test "plasma" was developed. It contained physiological concentrations of sodium chloride, glucose, urea, amino acids, triglycerides, linoleic acid, cholesterol, cholesterol ester, and phospholipid. Simple lipid pickup by samples agitated up to 8 weeks in the mixture at about 37°C plateaued at about 1.5%. The addition of oxidized linoleic acid products to the test mixture only minimally increased pickup, to 1.7%. As these polar compounds are not readily soluble in silicone rubber [5], a concept was developed that the oxidation products of polyunsaturated fatty acids are formed by the action of molecular oxygen on the fatty acids after their absorption into the rubber. This was validated in one experiment by bubbling oxygen into the test mixture with oxidized linoleic acid products. Balls that had plateaued at 1.7% showed increased absorption, with a yellow, opaque appearance and yellow focal areas. The same experiment, but without the oxidized products, showed no increase. In another experiment, balls impregnated with linoleic acid were exposed to an oxygen atmosphere at 38°C for 4 months, resulting in the orange-yellow surface, yellow interior, and fissures and swollen areas found in variant balls. Extracts from these in vitro balls showed the same analytical profile as material from clinical in vivo variant poppets.

The effects of silicone rubber cure, filler, and use of alternate elastomers were also investigated. After compression molding, the balls must be cured to remove vulcanization by-products and to stabilize the compound by heating the balls at a high temperature for a period of time. The cure used for the occluders for the SCDK and early model S-C was at 216°C for 16 hours. A series of tests using mild to severe cure conditions demonstrated that lipid pickup increased with the severity of cure, and that prolonged cure induced some degree of reversion and increased lipid absorption. Both increased filler content and fluorosilicone elastomer demonstrated lower pickup than the control. Mechanical limitations, such as hardness, rebound, and deformation, precluded use of fluorosilicone or increased filler. As a result of these tests, the cure of the occluder was changed to a "mild" cure of 8 hours at 121°C followed by 8 hours at 204°C to reduce the propensity for lipid pickup.

These findings do not fully explain the cause of variance. Variations in body chemistry alone could not account for variance, as polyunsaturated fatty acids and their esters are present in the blood of all valve recipients. Also, variations in silicone ball manufacture such as cure and filler content, although possibly aggravating the condition in some cases, would hardly be the sole cause. It is generally thought that lipid absorption and ball variance result primarily from aberrant flow patterns in

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the prosthesis. Turbulence and ball impact trauma probably influence polyunsaturate absorption by freeing fatty acids and esters from protein. As lipoproteins, or otherwise protein-bound, they are not absorbed by silicone rubber. Mechanical action in or around the prosthesis could cause denaturation of the complexes and freeing of the polyunsaturates, which could then be absorbed by the silicone rubber.

Design and Manufacturing Modifications to Minimize Turbulence and Impact

A number of design modifications were made. (1) The throat of the orifice ring was modified from a truncated V section (SCDK) to a radius of curvature (S-C) for streamlined flow. The struts were also faired into the ring to guide the ball into the throat with reduced impingement. (2) Control on ball sphericity was tightened to require concentricity within 0.002 inches, and diameter to ±0.010 inches of nominal size. (3) We found that the occluders increased about 0.4% in diameter between room temperature and 37°C, the operating temperature of the valve. Ball dimensions were then measured after at least five hours in a 37° to 40°C incubator. (4) The metal cages of the valves were manufactured to match a specific ball, and were finished to have a clearance of 0.002 inches over the largest ball diameter.

The complete series of changes, along with the use of the mild cure poppets, were introduced in September 1966 as the Present Model Smeloff-Cutter valve. The valve design has remained unchanged since then. Notably, to date, and with in excess of 25,000 valves in use, no clinically significant ball variance with the Present Model Smeloff-Cutter valve has been reported to the manufacturers (Mizoguchi A, Sutter Biomedical Inc, personal communication).

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In Vitro Testing of Heart Valves: Evolution Over the Past 25 Years

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The earliest method for in vitro testing of heart valves was described by Leonardo da Vinci in 1513 [1]. Ironically, it was in 1952, the year da Vinci's work was described by O'Malley and Saunders [2], that the first heart valve was successfully implanted in the descending aorta by Hufnagel. The incentive for conducting in vitro studies was provided by three subsequent developments: (1) successful mitral and aortic valve replacement by Starr and Harken, respectively, in 1960; (2) increased federal funding for heart valve research in the 1960s; and (3) medical device legislation in 1976. Without these catalytic forces, in vitro testing probably would not have developed as it has over the past 25 years.

In vitro testing and other bioengineering considerations are summarized in numerous books [3–7], beginning with the First Conference on Prosthetic Heart Valves in 1960, and various review articles [8–12]. Literally hundreds of articles describing in vitro tests have been published in the past 25 years; therefore, a complete summary is not possible here. This paper will attempt to highlight some of the major contributions.*

In vitro evaluation of prosthetic heart valves involves three unique types of test systems: (1) pulsatile flow (pulse duplicators), (2) steady flow, and (3) durability (accelerated wear testing). Pioneering designs of pulse duplication systems were reported by Davila in 1956 and Kolff and colleagues in 1959. Gorlin introduced a hydraulic formula, the "Gorlin Equation," for calculating valve area in 1951, which is used today for calculating effective orifice area during in vitro testing. In 1979, Gabbay, Yellin, and Frater introduced the concept of a performance index, which is the effective orifice area divided by the mounting diameter.

In 1965, Davey, Kaufman, and Smeloff described a pulse duplication system that was used for quantitative studies in the development of the Smeloff-Cutter valve. Wieting introduced a pulse duplication system in 1966, with revisions in 1969, using anatomically designed testing chambers and incorporating a pneumatic power unit (Vitamek) and a mock-circulating system designed by O'Bannon. This system was used to make normal and high-speed flow pattern movies and measure velocity profiles from flow pattern photographs, shear stress, pressure drop, and backflow for various heart valves. Kaster described a pulse duplication-analog computer system in 1968 that provided on-line data and was used in the development of several heart valves. A substantial contribution was made by Bellhouse in 1969 with the description of the fluid mechanics of the natural aortic and mitral valves, as studied in an aortic chamber with sinuses, and a left ventricular-shaped testing chamber with an expanding "rubber" bag. In vitro testing in the 1960s became much more quantitative than that of the previous decade.

Beginning in 1970, Wright described various pulse duplication systems and methods for analyzing the flow characteristics of heart valves in a piston-driven ventricular-shaped chamber and aortic arch model. The concept of energy loss across prosthetic heart valves was introduced by Olin in 1971. Stripling, Wieting, and Hwang designed a left ventricular-shaped chamber, and used the hot-film anemometer for measuring the velocity distal to the human mitral valve in 1972. Arabia and Wieting redesigned this left ventricular-shaped chamber and used it for analyzing the fluid dynamics of prosthetic heart valves in 1979. Closing forces of heart valves were measured by Keddie in 1978, and by Kinberger in 1979. A pulse duplication system was described by Swanson and Clark in 1977 that was later used for developing the concept of a performance index, defined as the sum of the percentage pressure drop power loss and the percentage backflow. Swanson and Clark also conducted studies of streaming birefringence across heart valves. The Canadian team of Scotten, Walker, and Brownlee entered the arena of in vitro testing in the 1970s. Their original hydromechanical pulse duplicator evolved in the 1980s to the "Superpump," which is programmable and computer-controlled to provide a very sophisticated heart valve analysis system. Numerous innovative studies have been reported by this group over the intervening years. An important contribution was made in 1977 by Cornhill, who first described a pulse duplication system incorporating a characteristic aortic resistance, a capacitance, and a peripheral resistance based on the lumped parameter model of Westerhoff.

The fruitful collaboration of Hwang and Reul resulted in the development of a pulse duplicator in the late 1970s that incorporates a flexible left ventricular bag compressed by a computer-controlled servo-hydraulic system. Modified versions of this system have been used by both Hwang and Reul independently to conduct numerous scientific investigations of heart valves, as well as cardiovascular fluid dynamics, using the hot-film anemometer and laser-Doppler anemometers. In the 1970s, Rainer and Christopher used a pulse duplicator and high-speed cine-

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* A complete bibliography of in vitro testing is in preparation, and will be available from the author.

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matography to analyze the dynamic flow behavior of heart valves.

A major contribution to in vitro testing grew out of the collaborative efforts of Yoganathan, Harrison, and Corcoran in 1979. After the untimely death of Corcoran, Yoganathan has continued actively studying heart valves using the latest technology provided by laser-Doppler, echo-Doppler, and color-Doppler echocardiography to analyze the in vitro fluid mechanics of heart valves and compare the results with in vivo hemodynamic data by close collaboration with cardiologists, including Harrison. Dellsperger and Wieting collaborated with Harrison in 1983 and introduced the concept of backflow dependence on heart rate and cardiac output. The team of Martin, Tindale, and Black began reporting investigations of heart valves in the 1980s. Important studies have been reported by Chandran in the 1980s, including hot-film and laser-Doppler anemometer measurements of velocities in a model aortic arch and left ventricular-shaped chambers for various heart valves. Contributions by Chandran include the investigation of the effect of valve orientation, the effect of blood analogue fluids on tissue valves, and the effect of wedging of aortic valves.

Steady-flow studies were introduced by Forrester and Wieting in 1969 to compare the fluid-flow resistance (pressure drop) of 45 different heart valves. Steady-flow studies have also been reported using the laser-Doppler anemometer by Yoganathan in 1978 for wall shear stress measurement, and by Chandran in 1983 for velocity measurement. Other investigators who have used steady-flow systems include Martin, Tindale, and Black (1981), Gabbay (1978), and Reul (1986). The exact correlation, however, between steady-flow and pulsatile-flow data has not been well established.

Durability of heart valves has always been a major concern. Unique accelerated wear test systems have been described by Steinmetz, Merendino, and Muller (1964), Koorajian, Pierie, and Starr (1968), Almond and associates (1974), Clark and Swanson (1978), Swanson and Clark (1979), Fettel, Johnson, and Morris (1980), Gabbay (1979), Martin, Tindale, and Black (1981), and Reul (1986). Each of these accelerated wear test systems has been used to conduct extensive durability tests of prosthetic heart valve designs.

Future in vitro testing will probably be focused on the following areas: (1) quality assurance testing during manufacturing; (2) heart valve closing forces and mechanics; (3) cavitation erosion of metals and ceramics used in prosthetic valves (Leuer, in 1986, described cavitation erosion of pyrolytic carbon heart valves used in artificial hearts. Pitting suggestive of flow erosion has recently been observed and reported [13] on explanted pyrolytic carbon heart valves; therefore, the possibility of cavitation erosion of pyrolytic carbon and other materials used in heart valves needs to be studied very thoroughly); and (4) in vitro modeling of flow-related factors and other transport phenomena contributing to the calcification of prosthetic valves. Of course, there will be many other areas discovered for investigation along the way.

In summary, in vitro testing must continue to apply all of the latest technological advances to expand our understanding of the function of heart valve replacements before implantation in humans, in order to find the "ideal heart valve."

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Pitfalls in Statistical Analysis of Heart Valve Prostheses

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Accurate and precise determination of the risks of postoperative complications is important for evaluating and comparing the clinical performance of artificial heart valves. We began prospective follow-up with our first heart valve recipient in 1960. During the ensuing years the research projects that this system permitted have made us aware of many statistical pitfalls, which can be grouped into five somewhat overlapping categories: (1) data acquisition; (2) series selection; (3) statistical methods; (4) automated analysis; and (5) interpretation.

Data Acquisition Pitfalls

The method used to acquire clinical information has a fundamental effect on its accuracy and completeness.

Retrospective Versus Prospective

If the decision to study a group of patients is made some time after their treatment has been completed, retrieval of important information must rely on the patient's memory of events that may be many years past, or the patient may be deceased at the time of the follow-up, eliminating his or her help in reconstructing the postoperative experience. The term retrospective is often used to describe this method, as opposed to a prospective system in which each patient is routinely followed as their postoperative experience unfolds, independent of any decision to conduct a study.

Passive Versus Active

Follow-up methods may range from passive to active, according to the effort invested in pursuing lost patients and causes of possible complications. This in turn affects the completeness of the follow-up, which can obviously affect conclusions, especially if the missing percentage could account for the difference between a good or poor performance. Follow-up completeness is often not given or, when it is, is not defined ("99% were accounted for"—as of when?).

Pipeline Effect

A problem that may plague even the best follow-up system is the lag between the occurrence of a complication and its reporting. The events reported in this month's journal have been in the "pipeline" between occurrence and publication for up to 2 years.

Definitions

A major pitfall has been the lack of standard definitions. A recent attempt to overcome this problem has been the concurrent publication of reporting and nomenclature guidelines in three surgical journals [1–3]. However, these general guidelines need a supplementary, detailed, working handbook to cover the complex situations encountered in practical use: for example, how to decide whether an infarction began before or during operation, and what date to use for death or follow-up when only the year is known.

Selection in Reported Series

Valve results that are published, and upon which we must base our knowledge of valve performance, may not be representative of, and therefore generalizable to, the general population of patients.

Case Selection Bias

The patients in a series may be selected by the decision of referring physicians, perhaps because of the experience or skills of the surgical group, or other factors. For example, this selection process has been seen to seriously curtail patient referral to a surgical center because of participation in a randomized clinical trial. A further selection occurs by the surgical team regarding whether to accept the patient for operation. And after the decision to operate has been made, a selection of the treatment type—eg, repair instead of replacement, or the type of valve to use when several types are used concurrently—must be made.

Publication Bias

The above types of bias determine which series exist for potential study; whether or not the series is in fact reviewed, or if reviewed, is submitted for publication, may be based on the results obtained. A series may be submitted because the results are particularly good or poor, depending on the physician's bias, eg, structural failures in a mechanical valve series might be the motivation to publish (or not). Finally, the decision to accept a series for publication may reflect another set of prejudices, that of the referees and editors.

Misleading Statistical Methods

The wrong statistical method for a given situation might be used, or the right statistic might be used improperly.

Ignoring Time Relationship

After heart valve replacement became a clinical possibility in 1960, the challenge to surgeons was to reduce the operative mortality. Over the next 5 years operative survival rose dramatically, from about 50% to about 90%, representing a rewardingly steep learning curve. When attention then shifted to late survival, it was still often

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described using a simple percentage. The realization of this pitfall led to almost universal acceptance of actuarial-type methods, but the misleading "late percent" is still occasionally used. Similarly, logistic regression, which is also designed for a dichotomous response variable, should not be used for time-related events such as survival. On the other hand, Cox regression should not be used for a non–time-related event such as operative death.

Linearized Rate for Nonconstant Risk

A linearized rate should only be used to summarize the risk of an event when that risk is constant over time (which corresponds to an exponential event-free curve). This is not the case for primary tissue valve failure, and may only be approximately true for events such as thromboembolism. In such cases, the hazard function should be used to measure the time-varying risk.

Multiple Comparisons

The p value of a statistical test measures the probability of observing such a difference by chance alone (and thus of falsely concluding that the difference is significant). When numerous tests are performed on the same data, which often occurs in clinical studies, the probability of this false conclusion increases, though the p value does not. One suggested correction, though rarely used in practice, is to multiply each observed p value by the number of p values generated (Bonferroni).

Improper Comparisons

Comparing groups that are not comparable with regard to the characteristics affecting valve performance can lead to erroneous conclusions. A conclusion opposite to the true one may be reached simply by the omission of one important covariate (Simpson's paradox). In fact, a prognostic factor should probably be accounted for in the comparison even if it is balanced in the groups being compared!

Pitfalls of Automated Analysis

A modern category of errors has arisen because of computer programs that make decisions arbitrarily, ignorant of the subject matter.

Misspecification of the Model

For example, in the Cox regression the assumed relationship between the hazard function and a linear function of the covariates is rarely tested. Transformations or recoding of the variables may be required.

Wrong Covariates Chosen

Important covariates may be absent from the model. The presence of an inappropriate covariate can reduce, eliminate, or reverse the effect due to another factor.

Outlier Data Points

Points with inappropriately high influence on the results may be from error or from abnormal subjects.

Unjustified Extrapolation

A model can be used recklessly to extrapolate beyond observed postoperative time, or to unlikely or impossible combinations of variables (pregnant and male).

Dangers of Interpretation

Statistical Versus Clinical Significance

When the p value resulting from a test of hypothesis is not small enough to imply statistical significance (eg, >0.05), this does not mean that "no difference exists" as is sometimes claimed, but only that the study failed to demonstrate one. A clinically important difference may exist in spite of the lack of statistical significance. Conversely, a statistically significant difference is not always clinically important; if a large enough sample is studied, every difference will eventually become significant.

Correlation Versus Causation

A significant correlation between two variables (eg, intraaortic balloon pump and operative death) does not mean that one was a result of the other, but may be due to the common relationship with a third, causative variable (poor left ventricular function).

Actual Versus Potential Failures

The actuarial percent of failures (eg, 70% tissue valve failure by 15 years) will not actually occur; the competing risk of death will eliminate many patients before their valve would have failed, resulting in a much lower percent of valves (about 40% by 15 years) that actually fail.

Valve-Related Versus Not Valve-Related

The intrinsic stroke rate is quite high in very elderly patients. This could distort the analysis of thromboembolism, especially for comparative purposes.

Small Percent of Variation Explained

Multiple regression analyses often find several variables highly significant, but together they typically account for only a small fraction (often less than 20%) of the total observed variation in the series, as measured by the overall R^2.

Over- or Under-Reacting to Rare Events

Random events are not uniformly distributed except when taken on a large enough scale relative to the occurrence rate. For example in a town with an average of seven accidents per week, the probability of a given week having one per day is 1/163, thus this would occur only once about every 3 years.

Summary

Beware of the dangers of automated analysis, especially in multiple regression, and of overinterpretation of data. Do not let yourself be manipulated by numbers.

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Prosthetic Heart Valves: Design Considerations

M. Tascon, MD

During the last 25 years great progress has been made in the area of heart valve design and replacement. In spite of substantial contributions in valve designs, a perfect valve is not available. Most of the available stented or supported protheses result in an orifice appreciably smaller than the natural valve and, in some cases, an unacceptably high pressure gradient. A high pressure gradient causes extra work for the heart, turbulence, blood component damage, and also valve deterioration. Because of these complications one must design a valve with the largest possible orifice area. Other disadvantages of tissue valves are the development of calcification, valve dysfunction [1, 2], and the need for valve replacement in 20% to 40% of the patients within a 10-year period [3, 4].

Reoperations of patients in whom prosthetic heart valves have been implanted are not free from complications [5]. The risk increases when an emergency procedure is necessary [6, 7]. Some of the complications that occur during reoperation may be related to the technical difficulties of excising the dysfunctional valve in the presence of severe scar tissue and calcification around the annulus. In an effort to minimize the occurrence of complications, my colleagues and I have developed a new porcine bioprosthesis with a detachable sewing ring that facilitates both insertion and removal.

Material and Methods

During the last several years, efforts have been made to maximize the inner diameter to outer diameter ratio of the porcine bioprosthesis by selecting stronger and thinner materials. We use flexible Elgiloy covered with a thin tubular Dacron polyester cloth for the stent. The overall thickness of the finished stent wall is under 0.5 mm. By reducing the stent wall thickness, a tissue valve one or two sizes larger can be mounted in the same size stent. A Delrin threaded locking mechanism molded to the Dacron cloth permits rapid attachment and detachment of the two components. The bioprosthesis is a low-pressure glutaraldehyde-fixed porcine aortic valve. The commissural angle of porcine aortic valves varies from valve to valve. Because of this, care is taken to match the right stent to the porcine valve tissue. A mismatch of the two components can lead to excessive stress on the tissue and valve failure. The bioprosthesis sewing cuff is stored dry in a separate sterile container, so it can be sutured in place while the porcine valve is rinsed. This design simplifies the suturing of the sewing ring, eliminates the possibility of suture entanglement around the stent posts, allows full visualization of the sewing ring sutures, and prevents drying of the valve tissue during implantation.

The valve was implanted in 30 animals (calf, goat, and sheep) at five institutions for periods up to 12 months. In addition, between March 1984 and June 1986 approximately 250 valves were implanted in patients at nine clinical centers under an Investigational Device Exemption from the Food and Drug Administration. The heart was approached using medial sternotomy, and the sewing ring was sutured into either the aortic or mitral position using continuous or interrupted sutures. The valve component was rinsed for the required ten minutes, while the sewing cuff was being sutured in place. The valve was attached to the sewing ring by a special holder.

Results

No obstacles or surgical complications were encountered during the implantation of the bioprosthesis in the animal laboratory or during the clinical study. The valve's locking mechanism worked well in all the aortic implants. In the mitral valve implants, rotation of the valve into the sewing ring is accomplished when the valve component is in the same plane as the sewing ring. Best results were obtained when the sewing ring was maintained a few inches away from the mitral annulus while traction was placed on all the sutures [7]. The valve can then be easily seated into the ring. Clinical evaluation of the patients at the completion of the study showed excellent improvements, and most patients resumed normal activities. Postoperative valve gradients and calculated valve orifice area compared favorably with those achieved with other bioprostheses.

Comment

The main objective of the study was to develop a bioprosthesis with a detachable sewing ring, which would facilitate insertion and removal (Figs 1, 2). Another important consideration of the design was accomplishing this objective without compromising the effective orifice area or the safety of the device. Improvements in valve design have lessened but not eliminated the incidence of primary prosthetic valve failure. This fact is especially true in the case of bioprostheses, which appear to have a shorter life span. Although the proper selection of patients and improved myocardial preservation have reduced the risk of operative repair of prosthetic valve failure, excision of prosthetic valves can cause trauma to the surrounding periannular structures, which can result in bleeding or even lacerations of the heart with increasing morbidity and mortality.

A detachable bioprosthesis that can be replaced quickly without disturbance to the sewing ring and valve annulus is a major advantage. To achieve this, a tool was designed

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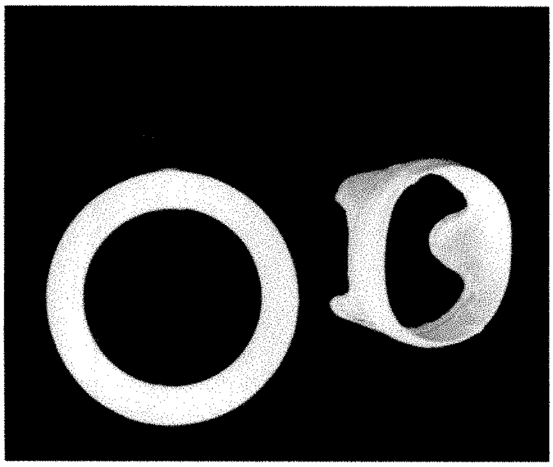

Fig 1. Valve stent and detachable sewing ring.

to facilitate the removal of the stented valve from the sewing ring without applying pressure to the annulus–tissue interface. A prototype was tested in the laboratory, and the valve was successfully removed in some animals. In other cases, however, fibrous tissue bridging the stent to the sewing ring in the ventricular side for the mitral valve was too strong for safe removal. Due to this difficulty, we modified the interface between the sewing ring and the stent. The Delrin threads were eliminated. The stented valve simply slides into a smooth metal ring and is sutured in place through three pairs of corresponding slots in the stent and sewing ring. Valve removal is accomplished with specially designed blades.

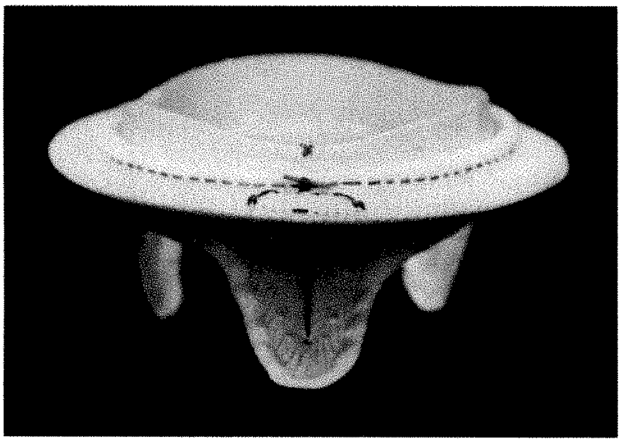

Fig 2. Assembled valve stent and detachable sewing ring.

This new design was tested in several animals at the National Institutes of Health. The bioprosthesis was easily replaced 4 to 5 months after the operation without disturbing the well-healed sewing ring. Cardiac catheterization of the animals intraoperatively and 4 to 5 months postoperatively revealed pressure gradients favorably comparable with those of other clinically available bioprostheses studied at our institution. We conclude that this valve design offers a simple procedure free from surgical complications.

In summary, further improvements in prosthetic heart valve development are contingent on the availability of newer and better materials or on improvements in existing materials. We can utilize available materials more effectively to produce devices that are more efficient in performance, blood compatibility, and durability. The new bioprosthetic heart valve described here, with its detachable sewing ring facilitating both insertion and removal without compromising valve safety or hemodynamic performance, is one example of how heart valve technology can be improved.

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Heart Valves: Ten Commandments and Still Counting

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> The ceremonial occasions of life have been so endlessly repeated that the wiser the observation they invoke the more time worn they are.
>
> Vermont Royster

So it is with prosthetic heart valves. We know where we want to go, but it appears to be nearly impossible to get there from here. In the 1950s I defined Ten Commandments for the prosthetic valve, still often quoted but not met.

1. It must not propagate emboli.
2. It must be chemically inert and not damage blood elements.
3. It must offer no resistance to physiological flows.
4. It must close promptly (less than 0.05 second).
5. It must remain closed during the appropriate phase of the cardiac cycle.
6. It must have lasting physical and geometric features.
7. It must be inserted in a physiological site (generally the normal anatomical site).
8. It must be capable of permanent fixation.
9. It must not annoy the patient.
10. It must be technically practical to insert.

Historical Perspective

In the 1950s, my colleagues and I had found some diseased valves that were impossible to repair. When debriding calcific aortic stenosis, we often debrided to no valve. Such crises caused us to work feverishly in the laboratory, where none of our animals survived aortic valve replacement with a prosthesis.

Hufnagel's chambered-ball valve in the descending aorta showed us several things: durability, acceptable sound level with silicone balls, and possibly (erroneously) acceptable thrombogenicity. However, physiologically the valve had to be beneath the coronary ostia where we thought a caged-ball valve could be implanted. Much work followed to determine the ball to base orifice ratio: if the height of the cage was too tall, there was too much regurgitation in closing; if the cage was too short, the valve was obstructive. Hufnagel gave us the silicone balls. The work also focused on pulse duplicators (a great assemblage of artifacts). Some accelerated wear studies were a further source of misinformation. We built a caged-ball valve that seemed reasonable. We feared that if the valve tilted, contact with the aortic wall might interfere with poppet movement, so we installed an outer cage. Starr showed this to be unnecessary.

Clinically we had extensive exposure to a malignant syndrome of aortic valve disease, ie, angina, syncope, and congestive heart failure unresponsive to medical treatment. We collected 87 such patients between 1950 and 1960. Seventy-seven were dead within 7 months. We did not have to have a perfect valve; we just had to have a good one.

At a hearing in Washington, DC, I was asked, "What is a safe device?" I answered, "A device is safe when it is safer than the condition it corrects." To that Dr Arthur Beall added, "And is the best available." These two responses are widely quoted as the definition of a safe device: "A device is safe when it is safer than the condition it corrects and is the best available."

Extensive experience (some of it quite unhappy) with open debridement and open valvoplasty taught us how to approach and implant prostheses. There were 2 survivors among the first 7 patients, 1 of whom had operation on March 10, 1960, and the other, June 6, 1960. Both have undergone valve replacement, 1 at 3 years for paravalvular leak and 1 at 22 years for bacterial endocarditis, and both are alive today.

The ball valve has been far less satisfactory in the mitral position. The ball, though isobaric with blood, still has inertia, and with low atrial opening pressures, inertia becomes important. Ball valves occupy considerable space and reduce stroke volume and cardiac output. In small ventricles, ball valves can obstruct the outflow tract and even produce arrhythmias and damage by impinging on the septum.

National Implant Registry

This is all history, but it does bring up the National Implant Registry. Like so many of you, I had reservations about having the problems with our device aired. However, that is what we must have. In fact, be the implant a valve, pacemaker, artificial joint, or whatever, it is wholesome to have a wide survey service. I find it impossible to personally cover the entire professional literature. The media broadsides often cause inappropriate alarm. Many of our patients with a pacemaker or valve have been frightened by nonspecific press releases. The National Implant Registry offers appropriate specificity and relief to the majority.

In short, I think we need more critical assessment of malfunction, and will cite one example of why I believe this. A 62-year-old housewife had a Harken low-profile

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mitral prosthesis placed in 1969. I had taken the dimensions of Bud Kay's Kay-Suzuki valve, which offered superb hemodynamics but had been known to cock. I copied his specifications, but rounded the silicone poppet edge for longer wear and impregnated the silicone with barium for wear evaluation by cinefluoroscopy. A wear study embraces a cinefluoroscopy in precise silhouette; flattening of the round atrial poppet edge indicates wear. The wear study in October 1988 showed no change during the past year. A month later, the poppet escaped. In an emergency operation in November, Dr Peter Marquis Siedl of Fort Myers retrieved the poppet and replaced the prosthesis with a St. Jude valve. Thanks to his genius, the patient is alive and well. We must have more sensitive signals for replacement. The studies of Matloff and Chaux have suggested that; the National Implant Registry has warned us.

Anticoagulation

Finally, I must discuss a blinding glimpse of the obvious. We heart surgeons as no other group are creating a crisis in anticoagulation. Safe anticoagulation is difficult if not impossible. The way it is conducted worldwide leaves much to be desired. The way we allow our patients to be managed on anticoagulation is alarming. The number of patients who assume that "I will be notified if the level of anticoagulation is not right" is appalling. Frequently, patients are not notified. Physicians go on holiday, and secretaries do not always transmit the laboratory reports. Reporting systems are not standard. Many patients have no idea of their prothrombin level or what that means.

I urge the adoption of a national program, the points of which are as follows:

1. Educate patients about the use of warfarin sodium just as diabetics are educated about diet and insulin. Anticoagulants are just as important and are easier to understand.
2. Prescribe Coumadin (crystalline warfarin sodium) only in 5-mg tablets. Regulation in multiples or fractions is safer than regulation by the many available pastel shades and sizes. Patients know how many tablets they take, not how many milligrams. This is especially important when patients change geographical areas or physicians.
3. Instruct all laboratories to give the prothrombin time results to the patients as well as to the physician, and to give this time in seconds (not percentages or ratios).
4. Strive for a prothrombin time, in seconds, 1.5 times the control. One and one-half times the control is easy to understand and has high and low safety margins. We formerly recommended two times the control or a little less. That made it too easy to drift dangerously upward. We are now assured by the anticoagulant oracles that a little less than 1.5 times the control is safe. It is not. It is too close to the dangerously low level. Strive for 1.5 times the control, and let the patients know it. Tell patients that if they drift more than 3 seconds higher or lower than this, they should call their doctor or their anticoagulation center.
5. Have all patients on a regimen of anticoagulants have a prothrombin time determination at least once a month and more often if it is unstable.
6. If anticoagulants must be electively reversed, taper them; in an emergency, use fresh frozen plasma, not vitamin K. As reversal is often associated with dental work, remember that a simple extraction does not necessarily require reversal but it does require antibiotic coverage when there are cardiovascular indications for anticoagulation. Stress this to patients.

Conclusion

I have defined the goals and described the start up that rocky road. I have saluted the National Implant Registry and stressed the need to be alert to the modes of valve malfunction. I have pled the cause of safer anticoagulation. We have worshipped at the shrine of the Ten Commandments for the prosthetic valve, but we are still counting. We are still sinners.

Where Is the Ideal Heart Valve Substitute? What Has Frustrated Its Realization?

Julio C. Davila, MD

Laboratory and clinical experience in cardiac valve operations and use of imperfect but serviceable valve substitutes over the past four decades have framed the general specifications for an ideal heart valve substitute. This report covers four major aspects of prosthesis characteristics. (1) Implantability: Essentially stable, viable tissue-to-prosthesis linkage is achievable with a porous fixation element. (2) Hemodynamics: Minimal resistance and efficient opening and closing are best attained with bioprostheses and homografts. (3) Thromboembolism: Thromboembolism is a persistent problem with mechanical valves. It is minimized by biological valves and abolished, experimentally, by appropriately encapsulated implants. (4) Durability: Mechanical valves are best. Tanned bioprostheses undergo "spontaneous degeneration"; untanned homografts are a little better. Knowledge and technology are needed to develop a synthetic leaflet membrane that possesses inherent physical, visco-elastic-rheologic properties of natural valve leaflets and is compatible with natural healing processes.

(Ann Thorac Surg 1989;48:S20–3)

The two questions posed in the title demand a third: what are the characteristics of, or the specifications for, the ideal heart valve substitute [1, 2]? I believe that in the past 41 years of valve surgery we have learned enough to answer the latter, but we have yet to meet those specifications. The compromises that have been made—imposed by limited knowledge, limited technology, hunch, or intuition—have, nevertheless, made possible the fabrication of serviceable valve substitutes with which many important lessons have been learned. I shall comment, all too briefly, on four topics that contain most of those lessons and encompass the determinants of the necessary specifications.

Implantability

Any device, to be acceptable, must be safely, easily, and securely implantable. The third requirement implies surgical attachment and permanent acceptance by the host tissues: a stable tissue to prosthesis linkage [3–6].

Four well-known methods have been used. (1) The first method is "multiple point fixation," described by Hufnagel and Harvey [7]. My colleagues and I [4] found a variation of this approach useful, using a mitral purse-string suture, to implant monocusp and caged-ball mitral valves in calves without cardiopulmonary bypass. (2) The second method is the ingenious "mechanical fixation" method of Magovern and associates [8]. Access to the valves and adequate time provided by modern cardiopulmonary bypass and myocardial protection make both of these techniques unneccessary. (3) The third method is direct suture of the implant to the host tissues; the use of free homografts by Ross [9] and Barratt-Boyes [10] is its most notable application. Although healing is not ideal (the graft tissues are never infiltrated by scar) the implant does become well-encapsulated. Direct suture is unsatisfactory for solid materials without an intervening porous element. (4) A porous fabric ring as the attachment element for solid and rigid ball valves was introduced by Harken and associates [11] and Starr and Edwards [12]. It is used, with minor modifications, in all modern mechanical and biological prostheses. It is compatible with the natural healing process and successful in achieving a good tissue to prosthesis linkage. An improvement could be gained if the entire stent or ring were constructed of felt (made of Dacron, Teflon, polypropylene, or graphite fibers of approximately 50 μm thickness, a random structure of individual fine fibers with excellent porosity, and a surrogate stroma), which encourages the nearly ideal "capture" of the implant in healthy scar tissue [3, 4, 13].

Several successful suturing techniques are in use. I prefer a figure-of-8 stitch, originally used in an experimental valve ring made of Dacron felt and having a V cross-section [14]. I have used the same suture in various mechanical and biological prostheses having a Starr-style sewing ring with excellent results over the past 20 years.

Hemodynamics

The device we seek must be a unidirectional valve that, within a physiological flow range, offers minimal opening resistance as well as negligible impedance and generates only minor, if any, turbulence. It should close without measurable regurgitation [1, 2, 15]. Experience since the introduction of the Harken [11] and Starr-Edwards [12] valves, 28 years ago, has confirmed that all valves having a central occluder (ball, disk, lentil, or conical in shape) impose higher than desired opening resistance and high impedance to flow, close with minor regurgitation, and generate chaotic turbulence [4, 16]. The tilting-disc valves, whether single-leaflet [17, 18] or double-leaflet [19], offer much improved hemodynamics, but turbulence is still a factor and the built-in regurgitation may be undesirable.

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The free homografts in the aortic position and the bioprostheses as mitral, aortic, or tricuspid valve replacements provide the closest approximation to natural hemodynamics that has been attained. The former are sometimes associated with regurgitation. The latter occasionally impose substantial resistance in cases of a narrow aortic root, due to the bulk of the stent.

Thromboembolism

This has been an obvious and difficult problem associated with implants in the cardiovascular system [4]. All mechanical valves demand systemic anticoagulation, with its attendant complications. Despite the use of such drugs, there is still an important incidence of fatal or disabling thromboembolism.

In mechanical valves, the preeminent cause of thromboembolism is the propagation of clot at the interface between tissue and nonporous (metal or plastic) elements of the device that are in direct contact with host tissues [3, 4, 13]. We were able to eliminate thromboembolism with experimental valves in which all elements to be in contact with tissues were made porous and susceptible to complete coverage (encapsulation) by scar tissue. In a final valve model, the occluder was made to be freely suspended within the orifice of the valve ring [14, 23]. This valve has other problems, notably hemolysis and a central occluder, but it demonstrated that thromboembolism can be controlled by valve design.

Use of free homografts [9, 10] has probably brought these complications to an irreducible minimum; the bioprostheses have had a similar effect [24, 25]. Both have permitted the elimination of anticoagulation in most cases. Both have demonstrated that despite a highly thrombogenic surface, bare collagen exposed directly to blood, massive thrombosis does not occur and embolism is rare. Probably most of those few embolic episodes that do occur are not valve-related. In the implanted bioprostheses, healing around the stent is free of the unstable, thrombus-susceptible interface noted for mechanical valves. An edge, or margin, of the cicatricial capsule extends onto the basal surfaces of the implant (aortic wall and base of leaflets), adhering well to the rough, bare collagen face (analogous to the gingival or paronychial margins) and thus remaining free of propagating clot. The absence of thrombus on the exposed collagen surfaces of the middle and distal parts of the leaflets is probably the result of their constant motion which makes them self-cleaning, as in the case of freely moving (unattached) mechanical occluders.

Durability

Perhaps the major improvement in the mechanical valves in the last 15 years has been the virtual elimination of wear in the most vulnerable part, the occluder. Introduction of Pyrolite for fabrication of the tilting-disc valves [17, 18] seems to have solved this problem. Fatigue of slender metal parts is probably insignificant; occasional fractures are most likely the result of random flaws associated with fabrication. Even the silicone elastomer balls of the Starr-Edwards [12] and Smeloff [26] valves have exhibited good durability. One specimen of my valve [14], explanted after 13 years, showed negligible wear of the self-suspended polypropylene occluder.

Various types of artificial valves made with pliable leaflets (fabrics or elastomers) have failed due to stiffening by scar infiltration (fabrics) and fatigue-fracture or rupture. The "fine leather" of the bioprosthetic leaflets has been remarkably more durable than synthetic leaflets, despite potential biodegradability. This is probably due to the structural/architectural features of the natural leaflets [3, 4, 27]; their viscoelastic characteristics; the distribution and order of loose connective tissue, elastin and collagen fibers, and bundles; and the three-layer construction and geometry.

The living leaflets stretch, contract, vibrate, flex, and wrinkle [28, 29], all highly traumatic mechanisms. The three-layer architecture suggests that the membranous leaflet is protected from flexion-fatigue by the ability of the outer layers to glide upon the intervening spongy layer, thus relieving the effect of compression forces on the concave side (elastic layer, elastin) and tensile forces on the convex side (holding layer, collagen) of flexing leaflet segments. The bundles and fibers of collagen and elastin, within their respective layers, also glide upon each other. The best features of each material are applied to good advantage: collagen for tensile strength, elastin for flexion and deformation, and the spongy connective tissue as a quasifluid medium that permits the necessary movement of all elements within the leaflet body.

After tanning, the porcine bioprostheses exhibit some loss of pliability or flexibility, but retain excellent tensile strength. This suggests that the cross-linking of collagen fibers stiffens the bundles and reduces the possibility of gliding movement of fibers upon themselves, within each bundle. Changes in the spongy layer (possibly protein denaturation) may also impair that unique "rheologic" property of the intact leaflet. The elastic layer seems to remain, at least morphologically, quite stable over time. The early change of spontaneous valve degeneration [30] is random and spotty degradation of collagen. Is this due to stress and strain? Is it primarily the result of extrinsic biochemical attack? Or, is it simply the progressive loss of integrity due to aging of the collagen fibers? The mechanisms and rates of deterioration and of renewal of the various elements of the leaflet's structure (their half-life during the individual's lifetime) are unknown. The untanned, free homografts seem to have a bit better durability than the tanned porcine valves. Without evidence of inflammatory or immune phenomena in the latter, do the former wear better because the visco-elastic-rheologic properties are less altered?

Conclusions

The lessons and experiences of the past four decades of valve surgery, some of which have been briefly and incompletely touched upon in this report, lead to some plausible conclusions.

1. We have learned to surgically implant heart valves safely and securely, attaining a very satisfactory tissue

to prothesis linkage with appropriate porous fixation rings.

2. Hemodynamically, the tilting-disc valves are adequate, but the biological valves are best.
3. The hazards of thromboembolism and of anticoagulation have been greatly diminished by the use of homografts or bioprostheses. The problems persist with all mechanical valves in current clinical use. Experimentally, it is possible to abolish this complication with a prosthesis that meets certain design criteria.
4. The durability of modern mechanical valves is excellent, but their thrombogenicity and anticoagulant dependency condemn the recipient to the hazards of embolism and hemorrhage for life. The performance of the biological valves has been excellent except for durability. In adults, re-replacement at 10- or 15-year intervals remains an option, but not a very attractive one. I doubt that a valve graft can be treated to last as long as desired (eg, 20 or 30 years). This would entail an implant that would retain intact its natural mechanical, rheological, physicochemical, and regenerative properties.
5. What has been accomplished has, by necessity, relied on limited understanding of the processes of tissue healing and a lack of means to manipulate them. The devices that have been fabricated to date have depended on available materials; materials developed for other, usually nonbiological purposes. Someone once said, in the early years of artificial heart valve research, that we had been making heart valves out of neckties. This, unfortunately, is still the case. But we are about to run out of neckties. I believe that without the development of new materials specifically designed to satisfy the specifications alluded to above—a very costly undertaking—we shall not see much more than minor refinements in existing mechanical prostheses.
6. We are also running out of basic scientific knowledge. Most of the advances in valve substitutes of the past 15 or 20 years have made use of information that was already available 20 or more years ago. These have been years of intensive application and not of much discovery.

The realization of a near-ideal heart valve prosthesis, acceptable small-caliber artificial blood vessels, a reliable artificial heart—among other items that interest the cardiac surgeon—depends on new knowledge and new materials. The specific need for the valve is a composite, synthetic leaflet (membrane, gel, fiber) that meets the specifications dictated by the natural valve leaflets themselves and by the phenomena of tissue healing.

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Early Years in Artificial Valve Development

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Various types of prosthetic heart valves developed and tested in the laboratory beginning in 1958 are described. Seven of such valves were implanted clinically in patients with congestive heart failure previously operated on by both the closed and open techniques in 1958 and 1959. The longest survivor was 6 weeks. Evidence is presented demonstrating that putting a film of polyurethane on the Teflon leaflet valve and fixation rings of disc valves reduces thrombosis, thromboembolism, and tissue overgrowth interfering with disc or ball valve function.

(Ann Thorac Surg 1989;48:S24–5)

In the field of valve surgery, it soon became apparent that a number of valves were in such bad condition, nothing but total replacement would suffice to provide correction. Research on prosthetic valve replacement began in 1958. During the subsequent 8 months, four mitral and three aortic valve replacements were done. The 4 patients undergoing mitral valve replacement had previously been operated on by both open and closed techniques. This experience and its problems were presented in June 1959 to the American College of Surgeons in Philadelphia and to the American College of Chest Physicians in Atlantic City.

First Artificial Valve Designs

The mitral valves consisted of Teflon fabric leaflets with a film of polyurethane and artificial chordae tendineae. The chordae were attached to the papillary muscles or were passed through them and fastened to the outer myocardium over Teflon pledgets. All plastics employed during the research developed fibrinous membranes of varying thicknesses. This problem was largely eliminated by giving the fabric a film of 15% polyurethane dissolved in tetrahydrofuran.

In the design in which the artificial chordae tendineae, made of threads of Teflon, were sewn to the papillary muscles, it was difficult to obtain the proper tension for leaflet coaptation. One patient lived for 2 weeks; at autopsy, the valve was in satisfactory condition. In 2 patients, the chordae tendineae were fashioned from cords of Teflon fabric passed through the papillary muscles and myocardium. After the heart was restarted, a finger inserted in the left atrium determined the tension needed on the chordae tendineae for leaflet coaptation. One patient with severe congestive heart failure underwent operation on May 4, 1959, and lived for 6 weeks. At autopsy, the valve appeared to be in satisfactory condition.

The 3 patients undergoing aortic valve replacement received a trileaflet Teflon valve that had a polyurethane film and was encased in a Teflon cylinder with coronary artery extensions for coronary artery transplantation. Cuffs of aortic wall were excised from the coronary ostia, to which the artificial coronary arteries were anastomosed while the patient was cannulated and perfused. The artificial valve was then sutured to the proximal and distal ends of the aorta. There were no long-term survivors. At autopsy, the coronary ostia were patent.

Subsequent Mitral Valve Prostheses

The subsequent mitral valve design consisted of a trileaflet Teflon valve with a polyurethane film that was inserted between solid Teflon fixation rings with semilunar extensions for commissural attachments. This model was used in 2 patients. One lived for 3 months and the second, 9 months.

The Starr valve was used for the next several years. My colleagues and I were disappointed in the outcome when it was placed in patients with small ventricular chambers because autopsy specimens revealed both inflow and outflow obstruction. To overcome this, we developed in 1963 a low-profile disc valve with a large fulcrum area (Fig 1). This valve was used in both the mitral and the aortic position between 1964 and 1974 (Fig 2).

Beginning in 1962, research and clinical trials involving aortic heterograft valves for use in the mitral position were conducted. Through a left atriotomy, the mitral valve of a dog was excised leaving a 3-mm cuff of leaflet tissue at the annulus to which the distal segment of the aortic valve graft was sutured; care was taken to position the commissures at appropriate sites. The proximal edge of the aortic valve was then sutured to the atrial wall.

In 20 patients with small ventricular chambers, aortic valve heterografts were placed in the mitral position. There were 6 operative deaths. The survivors experienced increasing regurgitation from leaflet fragmentation within 3 to 25 months, which resulted in death or replacement with a Kay-Suzuki valve.

Subsequent Aortic Valve Prostheses

Various aortic prostheses were developed between 1960 and 1962. Our first successful aortic valve replacement

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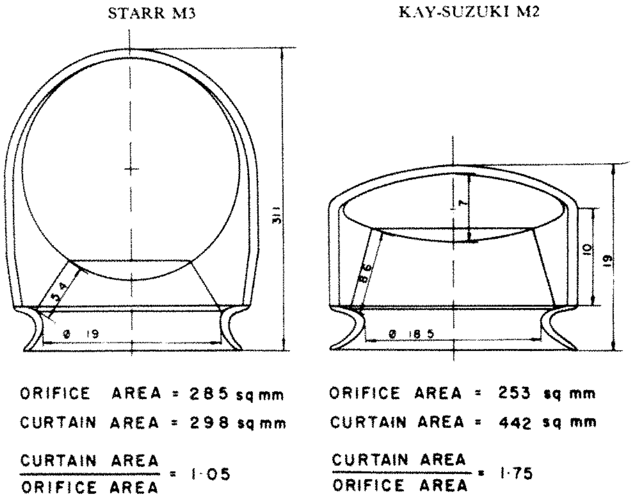

Fig 1. Kay-Suzuki disc valve with larger fulcrum area. (Reprinted by permission from Kay EB, Suzuki A, Demaney M, Zimmerman HA. Comparison of ball and disc valves for mitral valve replacement. Am J Cardiol 1966;18:504–14.)

with a Teflon-leaflet valve was performed in April 1960. Aortic regurgitation developed in 3 of 55 patients within 15 months postoperatively with this type of valve because of partial detachment of the commissures from the aortic wall.

To maintain commissural attachments, excess Teflon fabric at the edges of the leaflets was stretched into 2-mm cords 7.5 cm in length. These were passed through the aortic wall at the commissures. With the aortic root calibrator expanded, adjacent cords were tied in a circumferential manner about the aorta. Between 1961 and 1963, 130 patients were operated on with this technique. Anticoagulation was not employed, and there were no instances of thromboembolism. Though a number of patients enjoyed good health for up to 14 years, after a period of 3 to 5 years, the majority showed evidence of regurgitation caused by tears in the Teflon fabric. At reoperation, no substantial fibrous tissue overgrowth or thrombus was noted.

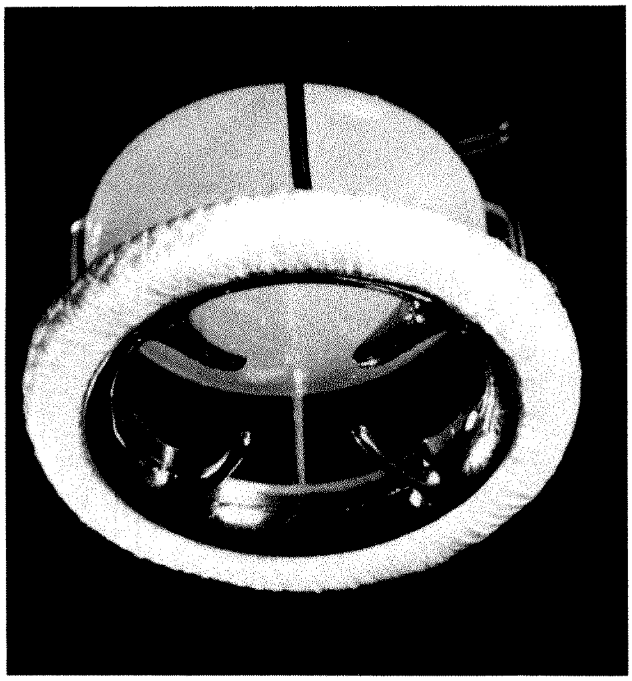

Fig 2. Kay-Suzuki disc valve. (Reprinted by permission from Kay EB, Suzuki A, Demaney M, Zimmerman HA. Comparison of ball and disc valves for mitral valve replacement. Am J Cardiol 1966;18:504–14.)

Thrombosis and Fibrous Dysfunction

Teflon-leaflet valves removed 10 or more years postoperatively were subjected to metallography with a microscope to determine the late status of the polyurethane-filmed Teflon trileaflet valves. The intact polyurethane film measured 0.4 mm in thickness and extended 0.06 mm into the interstices of the fabric.

Because we believed that polyurethane filming protected against fibrous proliferation and thrombus, sections of metal-fabric fixation rings were sutured into incisions made in the right atrial appendage of the dog. Those sections with a film of polyurethane showed no major fibrous tissue proliferation or clot, but specimens without a film demonstrated various degrees of proliferation.

Thrombosis, thromboembolism, and valve dysfunction from tissue overgrowth beginning at the fixation ring continue to cause concern. Providing the fixation rings with a film of polyurethane appears to reduce the tendency for these problems to develop.

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A Compression-Molded Leaflet Prosthetic Valve

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In the early quest for a suitable replacement device for the aortic valve, an attempt was made to mimic the central flow virtues of the normal anatomical valve. David Moore of the Research and Development Laboratory at the University of California, San Francisco, developed precision-machined steel molds for pressure injection of various extrudable materials. The molds were designed to distribute stress equally to provide uniform and equal leaflet thickness with sufficient flexibility to collapse with minimal forward thrust and enough tensile strength to resist physiological retrograde pressures. Apposition between cusps was deliberately limited to the leading edge to prevent curling. The performance of each model was studied in a pulse duplicator to verify competence and opening excursion and to correct imperfections in mold configuration (Fig 1).

A lengthy quest for a suitable material encompassed trials with Ivalon sponge, various synthetic rubbers, polyvinyl chloride, and ultimately a series of polymers (silicone rubber). Even at that time (1953) these compounds were available in numerous formulations, each of which

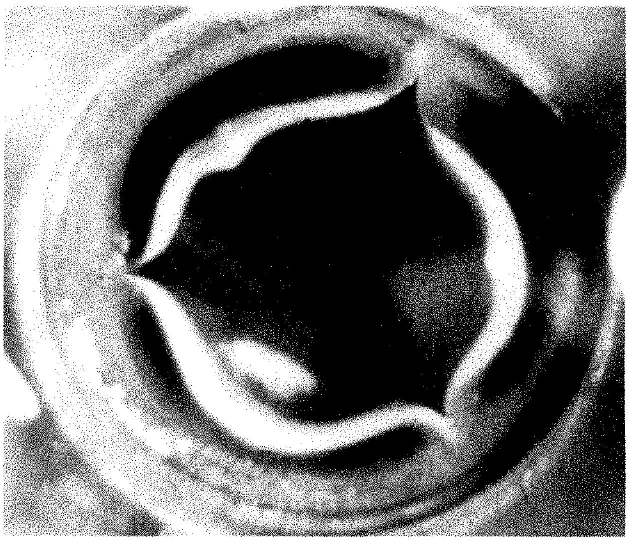

Fig 1. Distal view of the leaflet prosthesis in a pulse duplicator, demonstrating leaflet excursion and equality.

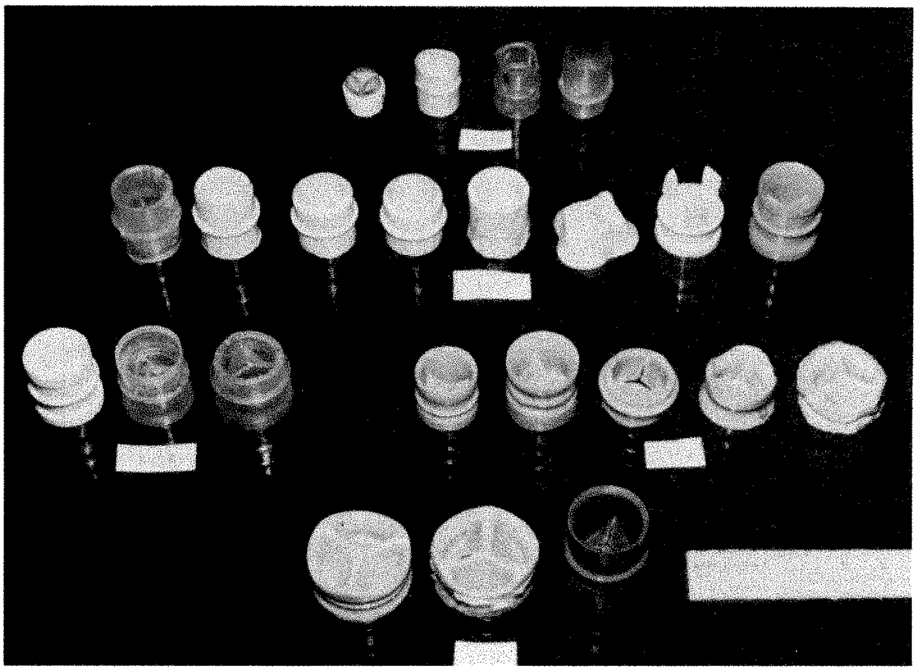

Fig 2. Historical series of experimental and clinical leaflet valves, all of which were products of compression molding. Various materials and configurations to facilitate implantation are demonstrated.

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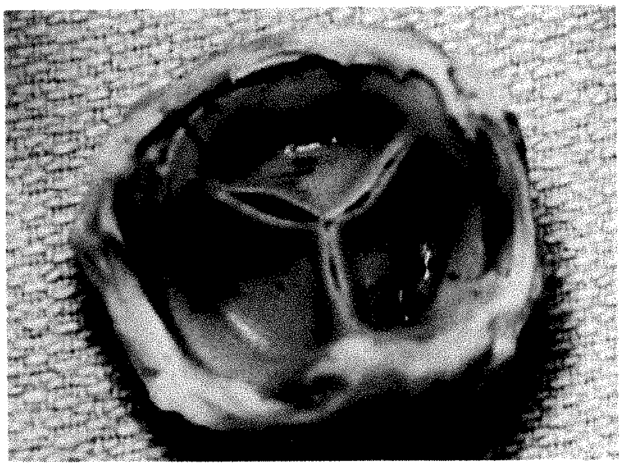

Fig 3. Explanted valve from a patient who died from a ruptured Berry aneurysm 6 years 10 months after implantation. A small thrombotic deposit is seen in one cusp and a 1-mm tear is present at one commissural attachment. Flexibility characteristics were unaltered.

could have its physical characteristics (tensile strength, elasticity, shear resistance, and ductility) manipulated by (1) molding pressure, (2) molding temperature, (3) curing duration, and (4) curing temperature. These numerous variables presented an almost infinite option potential, which we were able to explore only superficially. On the basis of catalogued information and some trial-and-error testing, we selected a General Electric elastomer for its tensile and ductal characteristics.

Animal testing began in 1954 with the three-cusp valve mounted in cylinders (Fig 2) that would maintain axial alignment in the aorta. These flexible models were folded and inserted through a descending aortotomy without benefit of circulatory arrest or cardiopulmonary bypass. The prosthesis was manipulated proximally to the ascending aorta, where it unfolded and was secured by sutures through the aortic wall. Thus durability and thrombogenicity was tested. Dogs survived with valves in this position for over a year without anticoagulation, although thromboembolic complications were frequent.

Subcoronary implantation became feasible with the advent of cardiopulmonary bypass, and castings were redesigned to provide suitable prosthetic configurations. Functional evaluation in this normal position provided sufficient information to support clinical trials.

The first human implantation was performed in July 1960, and a second one five days later. The first patient had valve dehiscence and died on the ninth postoperative day, but the second patient survived for 13 years. This experience led to improvements in the fixation material. Eight additional patients received valve prostheses: 2 died at operation, 4 died of late thromboembolic complications (because none were anticoagulated), and 2 were lost to follow-up. One long-term survivor, who died of a ruptured Berry aneurysm, provided an opportunity for reexamination of the valve after 6 years and 10 months of satisfactory function, radiographically proven competence, and complete symptomatic relief (Fig 3). Regrettably, the valve was not recovered from the patient who survived for 13 years.

This project was abandoned—perhaps prematurely—when manufacturing product control was not successfully solicited and Starr-Edwards valves became available. This potential compromise between mechanical and tissue prostheses, which has lain dormant for 28 years, perhaps deserves reconsideration in light of the greater potential of modern materials and engineering expertise.

Development of a Carbon-Coated, Central-Hinging, Bileaflet Valve

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Between April 1963 and January 1966, 86 patients at the University of Wisconsin Hospital underwent aortic or mitral valve replacement, or both, with a carbon-coated, central-hinging, bileaflet valve. A 25-year follow-up has been obtained on 43 of these patients discharged with an aortic prosthesis, 13 patients discharged with a mitral prosthesis, and 2 patients discharged with double prostheses. The mean implantation time was 7.2 years, 9.0 years, and 9.5 years, respectively. The longest aortic valve implantation time was 24.2 years in a patient who had her bileaflet valve prophylactically replaced, and the longest mitral implantation time is 24 years in a patient who is doing well with her original prosthesis. We are not aware of any patient among the approximately 700 receiving this valve around the world who has developed fatigue-failure of the silicone-impregnated Teflon fabric leaflet. This valve has demonstrated unexpected durability and has provided some design and biomaterial concepts that are used in a number of current prosthetic valves.

(Ann Thorac Surg 1989;48:S28–30)

In the early 1960s, the first prosthetic valves that were available for replacement of the mitral valve were fairly bulky caged devices containing either a ball or disc. The early Starr-Edwards ball valve was hemodynamically satisfactory for most patients with mitral stenosis, but we observed on occasion, in those patients with a normal-sized left ventricle, impingement on the septum by the cage with resulting ventricular irritability. We therefore considered a number of different new valve designs, principally of the leaflet type, to achieve a low profile contour. After experimenting with several prototype models of peripheral hinging leaflet valves, we settled on a valve with a Lexan (polycarbonate) housing and a central-hinging, composite leaflet of silicone rubber and Teflon fabric [1] (Fig 1).

Development of the Carbon-Coated Housing

Initially our bileaflet prosthesis was implanted in the mitral area of dogs, and we found that thrombus formation occurred on the Lexan valve housing within a matter of hours. We then developed an inferior vena cava ring screening test [2], and evaluated a number of different polymers, finding that virtually all of these rings thrombosed within two hours in the canine vena cava. Knowing from the work of Sawyer and Pate [3] that the lining of a blood vessel appeared to have a negative charge, we attempted to construct a valve with a conductive surface that could carry a negative battery charge. This concept was tested by dip-coating vena cava rings in a conductive paint of colloidal graphite and connecting the negative pole of a 9.4-V battery to the surface of the ring and the positive pole to the skin by means of an electrode. We found that the graphite-coated rings with the negative charge remained open for at least 2 weeks; however, one day the wire from the battery broke and the results were just as good without the negative charge. It took us nearly a year to determine that this exceptional thromboresistance was secondary to the fortuitous bonding of heparin to the graphite surface. We were using benzalkonium chloride to sterilize the graphite rings and were rinsing all of the rings in heparin before implantation. The relatively porous nature of the colloidal graphite coating was physically bonding the benzalkonium chloride with its positive charge and this, in turn, was forming a gelatinous salt with the very negatively charged heparin [4].

The graphite-benzalkonium-heparin coating was then applied to the Lexan housing of our bileaflet valve. This

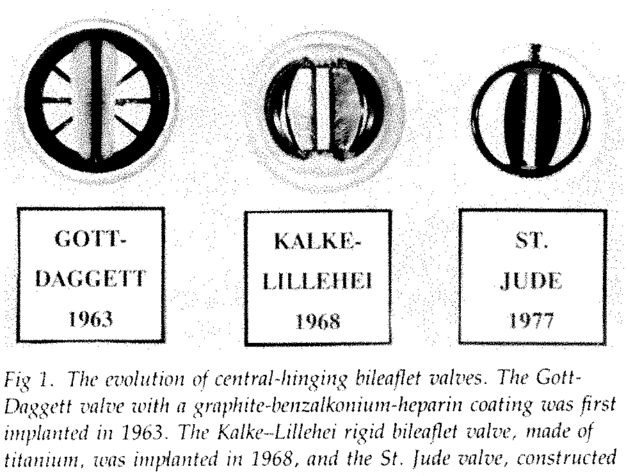

Fig 1. The evolution of central-hinging bileaflet valves. The Gott-Daggett valve with a graphite-benzalkonium-heparin coating was first implanted in 1963. The Kalke–Lillehei rigid bileaflet valve, made of titanium, was implanted in 1968, and the St. Jude valve, constructed entirely of Pyrolytic carbon, was first implanted in 1977.

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resulted in excellent long-term function of the valve in the mitral area of dogs [5].

Clinical Results at the University of Wisconsin With the Carbon-Coated Bileaflet Valve

The first of these graphite-benzalkonium-heparin–coated prosthetic valves was implanted by Dr William P. Young at the University of Wisconsin on April 30, 1963, in the aortic area. Over the next 3 years a total of 86 patients had the bileaflet valve implanted in both the aortic and mitral areas.

Our main concern at the time of implantation of this valve was related to the durability of the silicone-impregnated Teflon leaflet. There had been reports of deterioration of the silicone balls in Starr-Edwards valves, and we were hopeful that we could get 5 years of "flex-life" out of our leaflets. It has been gratifying that some of these valves implanted at the University of Wisconsin and elsewhere around the world have been functioning well for over 24 years, and we are not aware of a single instance of failure of the silicone-coated Teflon leaflets secondary to material deterioration. With an average of 40 million flexions a year, there could be well over 1 billion flexions in some of these valves in position for more than 24 years.

There have been a few reported instances of superstrut detachment with the loss of the leaflet. The superstrut fixation to the main valve housing was by means of a tiny polymer protrusion extending into the housing. It appeared that in some instances the application of the colloidal graphite solution with its solvents to the superstrut led to some weakening of this fixation site.

From April 30, 1963, until January 13, 1966, there were 46 patients discharged from the University of Wisconsin Hospital with an aortic bileaflet valve, 19 with a mitral bileaflet valve, and 2 with aortic and mitral bileaflet valves. Four of the 46 patients with aortic bileaflet valves also had a mitral ball valve placed. Late follow-up in the 67 patients was described in detail at an international prosthetic valve symposium in 1968 [6]. At that valve symposium we reported 16 late deaths (34.8%) in the aortic valve group, four late deaths (21.1%) in the mitral group, and no late deaths in the double-valve group. The causes of death in the aortic valve group included clotted leaflets (2), myocardial fibrosis (5), dislodged superstrut (3), bleeding (1), embolism (1), unexplained causes (2), and unrelated causes (3). Causes of death in the mitral group included clotted leaflets (3) and unexplained causes (1).

Now, 25 years after the implantation of the bileaflet valve at the University of Wisconsin, we have been able to find late survival data on 43 of the 46 patients discharged with aortic valves, and 13 of the 19 patients discharged with mitral valves. The mean duration of aortic valve implantation in the 43 discharged patients was 7.2 years, with the longest aortic bileaflet valve in place for 24.2 years (this patient received a Medtronic Hall aortic valve in July 1988). Another patient is alive and well at age 82, 22.2 years after implantation of her bileaflet aortic valve. Twenty-three of the 43 patients with the bileaflet aortic valve lived beyond 5 years (59%) and 13 lived beyond 10 years (30.7%). Five of these 43 patients had successful replacement of their bileaflet valve implant with a newer type of aortic prosthesis after an average interval of 10.7 years.

We obtained 25-year follow-up data on 13 of the 19 patients who were discharged from the University of Wisconsin Hospital with the bileaflet mitral valve. The mean duration of implantation in these 13 patients has been 9 years, and the longest implantation is 24 years in an individual who is currently alive and well. Eight of these 13 patients with mitral valves were alive at 5 years (61.5%), and 5 were alive at 10 years (28.5%). Six of the 13 patients that we have late data on had successful replacement of their bileaflet mitral valve with a newer mitral prosthesis after a mean interval of 12.7 years. Two patients with aortic and mitral bileaflet valves survived for a mean interval of 9.5 years.

The major problem with this valve was related to the fairly universal formation of the small amount of thrombus on the superstrut. This should have been anticipated because of the stagnant area of blood flow in the central portion of the downstream side of the leaflet. Fortunately, however, the thrombus was usually so minimal that it did not interfere with the hemodynamic properties of the leaflets.

Postscript

Although this valve was used in only 86 patients at the University of Wisconsin between 1963 and 1966, and probably in fewer than 700 patients around the world, its design and biomaterial concepts have contributed to some of the features in current prosthetic valves.

The presence of thrombus in the leaflet-hinging area of our valve was eliminated with a giant step in bileaflet design that was incorporated in the Kalke–Lillehei valve [7]. This later valve, first constructed of stainless steel for animal implantation and then of titanium for its first and only clinical implantation in May 1968 at Cornell Medical Center by C. Walton Lillehei, took advantage of the low-profile bileaflet concept but provided streamlined, nonstagnant central flow over both rigid leaflets (Fig 1).

The graphite-benzalkonium-heparin coating attracted the attention of Dr Jack Bokros of Gulf General Atomic in 1965. Bokros had developed a pyrolytic carbon material for the encapsulation of nuclear fuels, and contacted Vincent Gott in 1965 regarding the possibility of bonding heparin to his new material. Canine vena cava rings were constructed of the Bokros pyrolytic carbon, and it was subsequently determined that it was ineffective in bonding heparin because of its very dense, nonporous structure; however, it turned out to be the most thromboresistant, rigid biomaterial that we had evaluated in our canine ring test [8]. In fact, we are not aware of any rigid biomaterial now, 23 years later, that has better thromboresistant properties than pyrolytic carbon.

Initially, pyrolytic carbon was used cautiously in the fabrication of ball and disc poppets to be placed in metallic valve housings. Then a major breakthrough occurred in 1973, when Manual Villafana of St. Jude Medical adapted the Kalke-Lillehei titanium bileaflet valve configuration for the fabrication of a somewhat similar valve constructed entirely of pyrolytic carbon [9] (Fig 1). The construction of this new St. Jude valve demonstrated that all components of a valve prosthesis could be fabricated of pyrolytic carbon. Since the introduction of the very successful St. Jude valve a decade ago, Bokros' pyrolytic carbon has clearly established itself as the biomaterial of choice for all prosthetic valve construction.

In summary, our carbon-coated, central-hinging, bileaflet valve, which was first implanted in 1963, has demonstrated unexpected durability 25 years later. Also, it has provided some design and biomaterial concepts that are used in a number of current prosthetic valves.

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Comparative Study of Heart Valve Design in the 1960s

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The activity of my associates and myself in the designing of heart valves in the early 1960s was based on the principle that turbulence and stasis were largely responsible for thromboembolic complications as seen with the autologous mitral valve deformed by rheumatic valvulitis. It was evident that these factors also affected the efficiency of flow and the gradients developed across valves. Early studies measured only forward flow and gradients, thus ignoring the profound effects of pulsatile flow on valve design. The efforts of our group focused on three aspects of research: anatomical, engineering, and animal laboratory studies [1]. These studies were frequently simultaneous, but all the evaluations have led to an outstanding record of durability for our finished prosthesis. Early comparison of our design concepts with those of existing prostheses seemed sensible.

Anatomical studies using Silastic (Dow Corning) casts of the mitral and aortic annulus area, the left ventricular chamber, and the aortic root with the coronary orifices defined limitations in valve design. The study of the tricuspid orifice and the crescentic right ventricle allowed us to design a special prosthesis for use in the first correction of Ebstein's anomaly. Engineering principles [2] of valve design and flow through valves encompassed understanding of the "vena contracta" effect of sharp orifices restricting flow. The modification of the throat or orifice to minimize this effect also contributed to improved laminar flow eliminating eddies and turbulence. Overall size of the valve, particularly the ventricular portion, was pertinent to prevent the low output failure seen in the early Starr-Edwards valve.

Pulsatile flow studies emphasized the importance of a secondary valve orifice as measured by the area of the frustum of the right circular cone from the center of the ball to the orifice. Decreasing this area meant restriction of flow through the orifice; increasing the area by lengthening the cage resulted in increased regurgitation with decreased effective forward flow. The optimal ratio between the frustum area and the orifice area was found to be 1.0. A pulse duplicator was designed and constructed by Professors Davey and Kaufman at California State University at Sacramento using physiological pressures and wave contours to simulate the in vivo situation. High speed cinephotography of aluminum particles suspended in glycerin solution, corrected to the proper Reynold's number (viscosity) of blood, allowed careful study of flow patterns around valve prostheses. This arrangement also allowed comparison of flow gradients and regurgitation [3,4].

The evaluation of materials for use in valve prostheses encompassed several variables. Thrombogenicity of these substances was a paramount consideration. Inert, nonwettable materials with long clinical and research use were chosen.

Machinability of the cage material was another factor. Because it maintained its integrity during machining, titanium was selected. Its light weight and resistance to deformation were pluses.

A program of accelerated fatigue testing in the engineering laboratory was carried out as a mandatory requirement. These tests revealed surprising cage wear by other materials suggested for the ball such as Teflon and pyrocarbon.

Animal evaluation of the evolving prosthesis involved more than 100 implantations in mongrel dogs. Long-term survival up to 15 years was observed with mitral implants without anticoagulation. Postoperative catheterization studies revealed excellent hemodynamic variables with induced heart rates to 250 beats per minute. Seating of the ball was complete even at these high pulse rates, and cardiac output was maintained.

Comparative studies were begun by placing the Starr-Edwards ball valve, models A1200 and M1560, into our pulse simulator. They exhibited considerable bouncing of the ball off the orifice and actual fluttering of the ball in midstream at higher pulse rates. Pronounced regurgitation between bounces was manifested by "smoke rings" on the flow patterns. Stasis and reversal of flow distal to the ball at the crossing struts were seen.

The Gott-Daggett bileaflet valve was fascinating in that the leaflets opened only slightly during diastole in the mitral position, the flow spilling from them like waterfalls. There was almost total stasis between the open leaflets. These observations suggested flow restriction and probable early layering of fibrin on the leaflets followed by complete thrombosis. Later clinical results confirmed these observations.

With the Kay-Suzuki disc valve it was hoped to circumvent the inherent stenosis of discs by increasing disc travel. This would increase the frustum area about the occluder to equal the orifice area, as had been described in our previous work. However, when this principle was applied to a disc configuration, it permitted the disc to cock intermittently.

Our studies of the intriguing Davila valve showed closure of the poppet was irregular and suggested a woman pulling up her girdle. Its sealing of the orifice was also inconsistent. Good flow gradients were present.

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The Wada "hingeless hinge" valve revealed excellent function of the leaflet with some turbulence in the minor orifice. Early opening angles were excessive, retarding rapid closure. In response to the studies, the opening angle was modified, and this resulted in much more satisfactory flow.

The Cooley-Cutter valve used a pyrolytic carbon biconical disc in a full-orifice double cage. Flow patterns were improved compared with those of other disc valves.

The effective orifice of the Kay-Shiley valve was limited because of the short travel. This relative stenosis with the severe turbulence distal to the disc was predictive of severe thrombotic problems.

The ingenious concept of the Björk-Shiley free-floating disc introduced partial random movement of the disc. This eliminated the disc wear seen in the Kay-Shiley and Beall valves. Flow patterns were improved over previous disc valves. My colleagues and I were concerned about the durability of welded parts.

The multiplicity of parts of the Beall valve worried us, as we had previously decided on "unit body construction" for our valve. It also shared the flow restrictions and turbulence seen in the Kay-Shiley valve.

The Hancock porcine prosthesis surprisingly had erratic opening of the leaflets and rather narrow central flow with a fair amount of stasis in the area of the sinus of Valsalva.

The Braunwald valve had flow characteristics similar to those of the Starr-Edwards valve, but with elimination of the crossing cage struts.

As a result of all these studies, the Smeloff-Cutter valve was designed with a large cage machined from a single bar of pure titanium. Because of the design, casting, as is done with stellite, was considered undesirable. The throat allowed the ball to pass through the orifice from one cage to the other, allowing the largest orifice and smallest cage sizes to be used. This also eliminated the prominent bouncing on the orifice with the inherent regurgitation seen in the Starr-Edwards valve. An added feature was the washing effect of the potential stasis areas during valve closure. The Silastic ball allowed total random seating on the six small pads of the cage. Ball travel was optimized by making the secondary orifice or frustum area equal to the primary orifice.

Two later events influenced valve design. Prior to 1966, deformation of the Silastic poppets of the Starr-Edwards and Smeloff-Cutter valves occurred [5]. The Starr-Edwards ball became discolored, firm, and irregular in shape. Splitting with loss of the ball and actual thrombosis in the ball were noted. These findings prompted Dr Starr to consider Silastic an inappropriate material for use as a poppet and to explore the use of other materials such as stellite. Ball variance of the Smeloff-Cutter valve was found to include symmetrical swelling of the ball with yellow discoloration. Rather than abandon Silastic, chemical analyses were done and revealed that overzealous "curing" of the material allowed water-soluble elastomers to be retained. In vivo, this material was leached from the ball and replaced with lipids. Careful curing of the Silastic ball turned all the elastomers to elastic and totally eliminated this problem for the following 22 years.

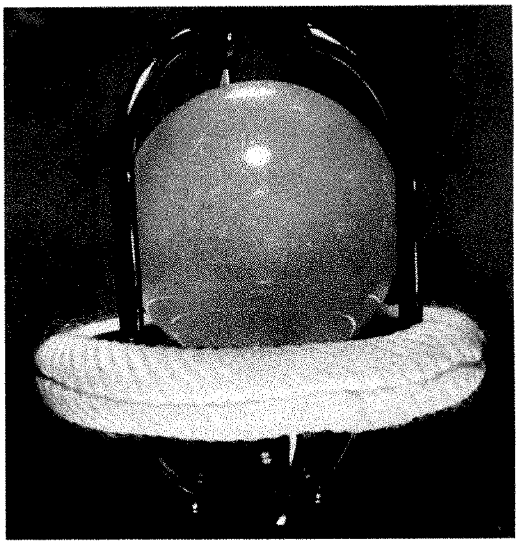

Fig 1. Current Smeloff aortic valve.

The second event to markedly affect the evolution of the valve design was the presentation by Dr Braunwald in 1966 of the totally cloth-covered Starr valve, the Braunwald-Cutter valve, which was implanted in calves. Our group did not follow suit for two main reasons. Dr Don Olson, veterinarian of the Desert Research Institute in Reno, advised us that prolific endothelialization of most graft materials take place in calves. We were also aware that abrasion of Silastic by fabric and fabric by Silastic could have dire consequences.

Clinical use of the present-model Smeloff prosthesis (Fig 1) includes more than 50,000 valves worldwide since 1966 [6, 7]. There have been only two instances of ball variance due to wear of the ball from errant sutures. No other structural failures of the valve have been reported during its 22 years of use. The incidence of thromboembolic events for fully anticoagulated patients has been 0.7% for the aortic prosthesis and 1.7% for the mitral prosthesis. Occlusive thrombosis of the valve has not been seen. The encouraging long-term clinical results with this valve have prompted our continued use of it.

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Twenty-five–Year Review of the Magovern-Cromie Sutureless Aortic Valve

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We reviewed 25 years (4,798 patient-years) of aortic valve replacement with the Magovern-Cromie sutureless valve. Operative mortality was 11% for isolated aortic valve replacement and 15% for aortic valve replacement with concomitant cardiac procedures. Since 1981, operative mortality has declined to 4.9%. Valve-related morbidity was in the lower expected ranges for prosthetic aortic valves: ball variance, 0.3%/patient-year; paraprosthetic leak, 0.41%/patient-year; valve endocarditis, 0.43%/patient-year; valve thrombosis, 0.04%/patient-year; and embolic events, 3.95%/patient-year. The incidence of aortic valve reoperation was 0.76%/patient-year. The 5-year, 10-year, and 20-year probability of survival corrected for normal mortality was 77%, 64%, and 52% for all discharged patients. This review confirms the Magovern-Cromie valve to be a safe, durable, and efficient prosthetic valve.

(Ann Thorac Surg 1989;48:S33–4)

From 1962 to 1988, aortic valve replacement (AVR) with a Magovern-Cromie sutureless valve was performed in 728 patients. The unique design of this valve comprises a barium-impregnated silicone ball in an open, three-strut titanium cage. It is inserted by rotating an implantation tool to engage multiple vertical pins into the aortic annulus. A central cylinder with an upper and a lower right-hand and left-hand thread is engaged to two titanium rings containing titanium pins. As the central cylinder rotates, the rings are approximated, thereby ejecting the fixation metal pins into the adjacent tissue (Fig 1) [1].

Material and Methods

Patient age ranged from 16 to 85 years (mean age, 55.6 years). Of the 728 patients, 564 (77%) were male. When first seen, 328 (45%) had aortic stenosis, 156 (21%) had aortic insufficiency, and 230 (32%) had mixed lesions. Fourteen patients (2%) had dysfunction of a previously placed prosthetic valve. Isolated AVR was performed in 591 patients. Concomitant procedures in the other 137 patients included coronary artery bypass grafting (84 patients), mitral valve procedures (119 patients), and mitral and tricuspid valve procedures (3 patients). Twenty-five patients had undergone previous aortic valve procedures.

Data were abstracted retrospectively from physician and hospital records. Follow-up, completed by November 1988, used a standard questionnaire directed to the patient, family, or referring physician. The incidence of complications is reported only for patients having isolated AVR or AVR with coronary artery bypass grafting, and represents 4,631 patient-years. Complications were attributed to the Magovern-Cromie valve unless another source was documented. Statistical tests included χ^2 analysis, analysis of variance, and life-table analysis (using BMDP software).

Results

Operative mortality (within 30 days of AVR) was 11% (67/591) for isolated AVR. With concomitant procedures, operative mortality increased significantly to 15% (21/137). Since 1981, operative mortality has declined to 4.9%. The major causes of operative death were cardiac failure (49 patients, 56%), arrhythmia (10 patients, 11%), thromboembolic events (11 patients, 13%), bleeding (9 patients, 10%), and complications due to aortic aneurysm (2 patients, 2%). Paraprosthetic leak resulted in one death, and before 1970, posterior aortic tear led to four deaths. Two deaths were due to gastrointestinal hemorrhage.

Six hundred forty patients were discharged, 52 of whom were lost to follow-up. Follow-up represents 4,798 patient-years overall. There were 346 late deaths, which were due to cardiac disease (including five sudden deaths) (175 patients, 51%), prosthetic valve failure (21 patients, 6%), noncardiac-related cause (52 patients, 15%), cerebral emboli (27 patients, 8%), and pulmonary emboli (2 patients, 0.6%). The cause of 69 deaths (20%) could not be confirmed.

Ball variance occurred in 14 patients (2%) and necessitated 12 reoperations with two deaths. Two cases were found at autopsy. The incidence of ball variance was 0.30%/patient-year. Prosthetic valve endocarditis was found in 20 patients (2.7%), an incidence of 0.43%/patient-year. Nine patients with prosthetic valve endocarditis required reoperation with five deaths. Three cases were discovered at autopsy. Paraprosthetic leak, excluding defects secondary to prosthetic valve endocarditis, was found in 19 patients (2.6%), an incidence of 0.41%/patient-

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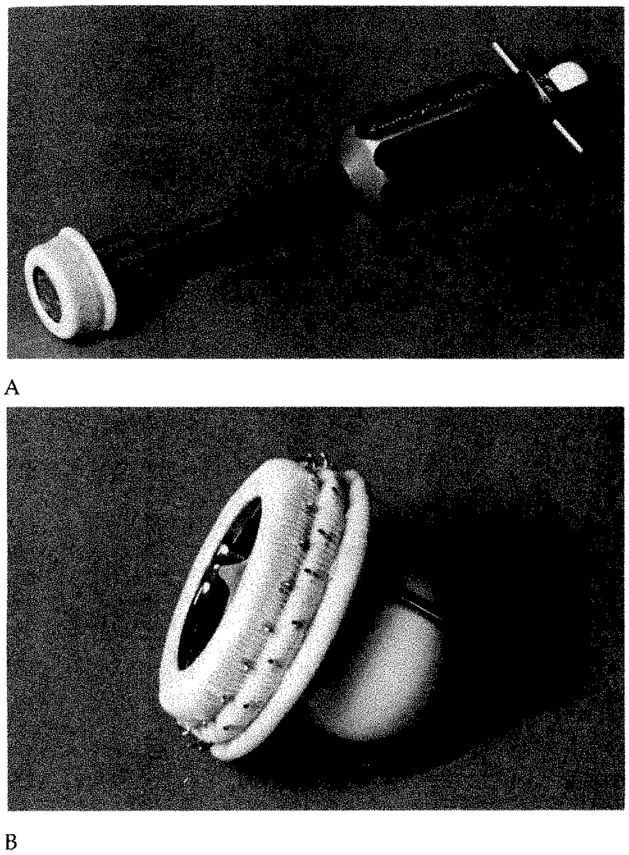

Fig 1. (A) Model A4 Magovern-Cromie valve with insertion handle. (B) Model A4 valve with vertical fixation pins extruded.

year. Four cases were discovered at autopsy, and 12 patients required reoperation with four deaths.

Total valve thrombosis occurred in 2 patients, an incidence of 0.04%/patient-year. One of these patients underwent reoperation and died. Multiple systemic emboli were the indication for one reoperation.

The average time to a second aortic procedure was 5.3 years (range, 0.2 year to 15.3 years). The incidence of aortic valve reoperation was 0.76%/patient-year.

There were 142 cerebral embolic events with 27 deaths, 22 peripheral events, eight pulmonary embolic events with two deaths, and 11 coronary artery emboli with four deaths. The incidence of all embolic events was 3.95%/patient-year. Permanent pacemakers were inserted in 88 patients perioperatively and in 31 during follow-up.

The 5-year, 10-year, and 20-year observed probability of survival for all discharged patients is 70%, 51%, and 28%, respectively. When corrected for the normal mortality based on Surveillance, Epidemiology, and End Results Program (SEER) 1980 data, the survival rate is 77%, 64%, and 52%, respectively. Survival at 5 and 10 years was increased for patients having isolated AVR compared with those having AVR plus a concomitant procedure (64% and 47% versus 55% and 38%). No difference was observed in 5-year and 10-year survival rates according to valvular lesion or thromboembolic complications. Five-year and 10-year survival was significantly decreased by the development of prosthetic valve endocarditis (44% and 23%, respectively).

Six weeks after operation, 97% of the 509 patients returning for evaluation were in New York Heart Association functional class I or II. Currently, 242 patients are alive and in follow-up. They represent 2,565 patient-years with an average survival of 10.3 years (range, 0.6 year to 25.8 years). Of these patients, 85% are in functional class I and 13%, class II.

Comment

A prosthetic valve is evaluated by simplicity of implantation, low incidence of morbidity, and durability. With its mechanical fixation, the Magovern-Cromie valve is remarkably easy to implant and routinely requires a cross-clamp time of less than 30 minutes [2]. Valve-related morbidity and mortality fall in the lower expected ranges for prosthetic aortic valves [3–8]. We attribute the low incidence of ball variance to slow curing and impregnation of the poppet with barium. Once the technique of mechanical fixation is mastered, valve placement can be easily checked and corrected if necessary, thus substantially reducing the incidence of paraprosthetic leak. Strut fracture, poppet dislodgment, and hemolysis were not seen in this review.

A disadvantage of the Magovern-Cromie valve may be a higher incidence of conduction defects in a population predisposed to atrioventricular dissociation due to severe aortic stenosis. Conduction complications can be reduced by careful sizing and choice of implant site.

We believe that this review confirms the Magovern-Cromie sutureless valve to be a safe, efficient, and durable prosthetic valve.

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The Origin and Development of Three New Mechanical Valve Designs: Toroidal Disc, Pivoting Disc, and Rigid Bileaflet Cardiac Prostheses

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During the 1960s three prosthetic valves of original design were developed to address problems with then-existing prostheses. The development of each progressed to human implantation. All have had complete freedom from structural design and wear failures. With today's hindsight, it is clear that each had an effect on subsequent valve evolution varying from modest to immense, as described herein.

Toroidal Disc

Design

This prosthesis was described in 1966 as the Lillehei-Nakib valve. It had a low profile and short travel, was fabricated from lightweight titanium, and added central flow for the first time to a discoid design (Fig 1A). In vitro hydrodynamic measurements [1] in an analog pulse duplicator system confirmed the superior flow of the toroidal design (with both central and peripheral flow) compared with the Starr ball valve and the Kay-Shiley discoid valve, both of which had peripheral flow only.

Clinical Results

Between 1967 and 1970 approximately 500 toroidal prostheses were implanted worldwide, mostly in the mitral position. Today, 18 to 20 years later, there has not been a single structural failure reported to the manufacturer (Washington Scientific Industries, Orono, MN), in the literature, or to the FDA. Early [1–3] and interim [4, 5] (4 to 8 years) follow-up results have been published. In addition, a personal series of 66 patients receiving the toroidal prosthesis in the mitral position has been followed (99% complete) for 17 to 20 years (3,178 patient-years). In this study the 30-day mortality was 17% (11 patients). There were 38 late deaths, of which 17 (45%) were valve related as follows: 11 patients, pannus/thrombosis; 3 patients, thromboembolism; 2 patients, endocarditis; and 1 patient, anticoagulant-related hemorrhage. At 17 to 20 years, a total of 16 patients (29.6%) are alive, and 5 patients (9.2%) are alive and event-free. Actuarial survival was 50%, 34%, and 22%, and freedom from thromboembolism and thrombosis was 77%, 67%, and 46% at 5, 10, and 15 years, respectively.

Lillehei-Kaster Pivoting Disc

Design

This original design, first described in 1967 [6, 7], introduced a free-floating pyrolytic carbon disc that opened to 80 degrees with a titanium orifice ring machined from a single block (Fig 1B). Additional features were the greatly improved central flow, rapid disc response, lifetime durability, relatively low profile, and rotatable Teflon sewing cuff.

Clinical Results

The substantial functional improvements in the pivoting disc prosthesis [8, 9] attracted widespread clinical acceptance, and 65,000 protheses were implanted in humans from 1970 to present.* Like the toroidal valve, there were no design changes once clinical usage began. This prosthesis design has had an exemplary reliability record. There has not been a single reported incident of dysfunction due to wear. Further, in this vast experience there have been only three instances of disc escape,* one at 3 months (aortic), one at 3 years (mitral), and one at 6 years (mitral) [10]. All 3 patients had emergency reoperations, and the 2 with mitral prostheses have been long-term survivors. In the patient in whom the retrieved disc fragments were studied by scanning electron microscopy, it was concluded that there was a flaw in the manufacture of the carbon disc [10]. This safety record of the Lillehei-Kaster pivoting disc valve is in marked contrast to the hundreds of deaths due to premature mechanical failure of the Björk-Shiley tilting disc prostheses [11] in a similar time span.

There have been more than 100 published reports on clinical results with the Lillehei-Kaster pivoting-disc valve. Thevenet and Albat [12] have recently completed a 10- to 13-year follow-up (99.6% complete) of 277 patients receiving 339 prostheses in aortic, mitral, or double valve regions. Actuarial survival percentages were 76.8, 64.4, and 59.1 for aortic valve replacement and 79.6, 67.2, and 54 for mitral valve replacement at 5, 10, and 13 years respectively. At 13 years, 70.1% of the patients who

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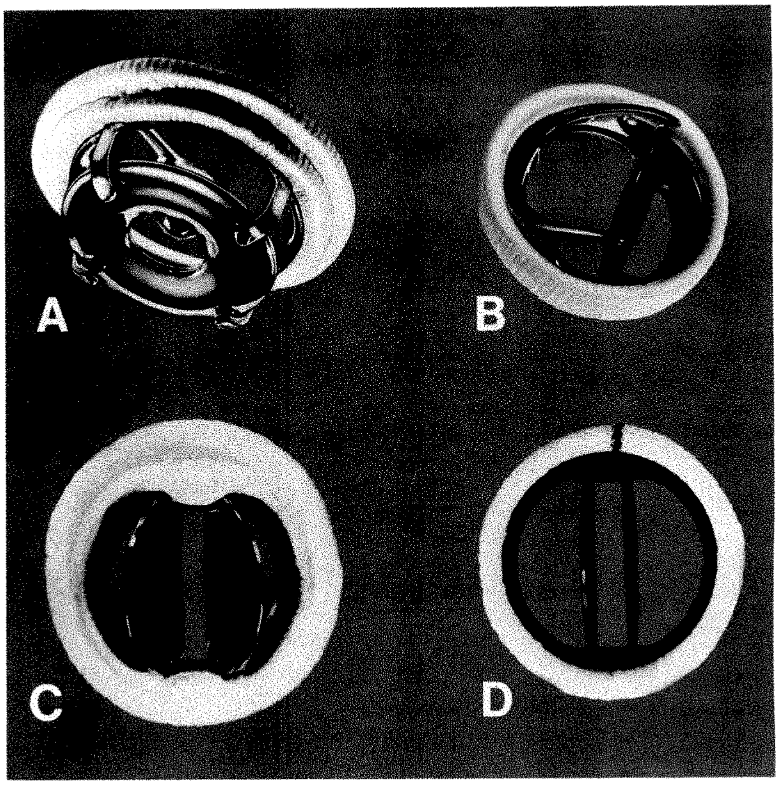

Fig 1. (A) Lillehei-Nakib toroidal discoid prosthesis (mitral position). All titanium. (B) Lillehei-Kaster pivoting disc valve (aortic position). Pyrolytic carbon disc, single-block titanium orifice, Teflon cuff. (C) Kalke-Lillehei rigid all-titanium bileaflet prosthesis (1968 Model), viewed from outflow side, fully opened (60 degrees). Teflon cuff. (D) All pyrolytic carbon, low profile St. Jude Medical prosthesis (1977), viewed from outflow side, fully opened (85 degrees). Dacron velour cuff.

received aortic valve replacement and 68.1% of those who received mitral valve replacement were event free.

Kalke-Lillehei Rigid Bileaflet Prosthesis

Design

This original design was conceived in 1965. Although the initial prototypes were very crude, this design captured our attention because it gave the best hydrodynamic performance in our analog pulse duplicator of any mechanical or tissue valve studied. Subsequent in vitro and animal implantation studies [13, 14] refined the design to the 1968 model [15] (Fig 1C). This prosthesis had a low profile and was all titanium, with the leaflets opening to 60 degrees. As the leaflets opened they moved apart to create a central orifice, thereby eliminating stagnation and improving central laminar flow. Each leaflet had two short cylindrical cams that rotated within a semiopen ovoid recess in the orifice ring. A series of titanium models were handcrafted by Harry Cromie (Surgitool Co, Pittsburgh, PA) and one of these was used in the first and only clinical implantation.* A search at that time for a commercial manufacturer was not successful.

Clinical Results

On July 4, 1976, a new company, St. Jude Medical, was organized by Manuel Villafana for the sole purpose of manufacturing a rigid bileaflet prosthesis. The configuration of the Kalke-Lillehei titanium valve was refined and improved on in several important ways. The titanium was replaced by pyrolytic carbon, the leaflet opening angles were increased to 85 degrees, and the pivot mechanism was made more open to washing during both systole and diastole [16]. The first clinical implantation of the St. Jude Medical prosthesis (Fig 1D) occurred on October 3, 1977, the 100,000th implantation in 1985, and the 200,000th implantation (more than any other prosthetic valve in history) in September 1988. The design has remained unchanged. This rapid clinical acceptance, along with a published bibliography of more than 900 titles, testify to the unsurpassed performance of the St. Jude Medical mechanical prosthesis.

Conclusion

In summary, current evaluation of these three innovative designs introduced two decades ago indicates (1) the toroidal disc demonstrated lifetime durability and improved hemodynamics, but the discoid design was destined for obsolescence; (2) the pivoting disc design exhibited further improvements in hemodynamics, lifetime durability, and a low incidence of thromboembolism, and introduced pyrolytic carbon into widespread clinical usage; and (3) the rigid bileaflet design has had an immense influence on further improving hemodynamics and continued lifelong reliability, and has reduced valve-related complications to the lowest levels yet.

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* On May 20, 1968, a woman with advanced rheumatic mitral valve disease, recent bacterial endocarditis, and recent bilateral femoral embolectomies had mitral valve replacement. A Kalke-Lillehei prosthesis with an inner diameter of 20.5 mm and an outer diameter of 29 mm was used. Postoperatively her condition was satisfactory for 24 hours, at which time low output appeared and was unresponsive to treatment. Death occurred at 48 hours. At autopsy, it was not possible to determine the cause of death.

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Wada-Cutter Heart Valve: Overall Experience at the Sapporo Medical College

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We performed cardiac valve replacement using the Wada-Cutter valve in 124 patients during the 9 years between 1966 and 1974: aortic valve replacement in 48, mitral valve replacement in 56, tricuspid valve replacement in 9, and multiple valve replacement in 11. Sixteen patients died within 30 days after operation, and 34 died in the late postoperative period, with a cumulative mortality rate of 40.3%. Postoperative complications included valve thrombosis in 9 patients, thromboembolism in 4, and mechanical valve failure in 5. The Wada-Cutter valve, first described at the Annual Meeting of The Society of Thoracic Surgeons on January 27, 1967, in a discussion on the paper by Cooley and colleagues on mitral valve replacement with a discoid valve, attracted attention for its unique design. Four of the Wada-Cutter valves were incorporated in Liotia's total artificial heart, which was implanted clinically for the first time in Cooley's second-stage heart transplantation. It may not only claim to be the origin of today's most popular tilting-disc heart valves but also has some original concepts with regard to bileaflet and tricuspid tilting-disc heart valves. However, at that time, cardiac valve replacement with this prosthesis resulted in a high incidence of thrombosis without systemic anticoagulation and in mechanical valve failure due to hinge wear of the Teflon occluder. For these reasons, its clinical use was discontinued in 1974. If Pyrolite carbon had been adopted in construction of the valve when it first became available, the valve design could have been useful even today.

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Since cardiac valve replacement using a ball valve was first performed in the aortic position by Harken in 1960, various cardiac valve prostheses have been developed and applied clinically. In 1966, Wada and associates [1, 2] designed the Wada-Cutter valve, which had a smaller intracardiac space occupation than the conventional ball valve and a more central flow with a more minimal pressure gradient than disc valves, and attempted its clinical use. This study evaluates the long-term results of cardiac valve replacement using the Wada-Cutter valve, which was the prototype for the tilting disc valves that subsequently became popular [3–6].

Material and Methods

The Wada-Cutter valve consists of a metallic ring of titanium, an occluder of a solid, hard Teflon, and a sewing ring of Teflon. Two notches on the occluder were engaged by two claws on opposite sides of the internal surface of the metallic ring, allowing opening and closing of the occluder. The maximum opening angle of the occluder was 75 degrees according to extensive flow studies by Professor M. Arie of the Hokkaido University School of Engineering (Fig 1).

Wada-Cutter valves were implanted in 124 patients admitted to the Sapporo Medical College and Hospital between September 1966 and September 1974 [1, 2]. The patients were aged 7 to 56 years (mean age, 39.9 years) and included 58 males and 66 females. The surgical procedure was aortic valve replacement in 48 patients, mitral valve replacement in 56, tricuspid valve replacement in 9, and multiple valve replacement in 11. Mitral valve repair was performed concomitantly with aortic valve replacement in 7 patients and with tricuspid valve replacement in 4 patients. Multiple valve replacements were aortic and mitral valve replacement in 5 patients, mitral and tricuspid valve replacement in 4, and aortic, mitral, and tricuspid valve replacement in 2. The preoperative cardiac function according to the New York Heart Association classification was class III in 77 patients (62%) and class IV in 48 (38%).

The prosthesis was fixed to the annulus by the continuous or knotless suture technique to eliminate numerous knots and suture cut ends as advocated by Wada and co-workers [7]. None of the patients who underwent Wada-Cutter valve implantation received anticoagulation therapy postoperatively. A follow-up study of the recipients of Wada-Cutter valves was performed at the end of 1976, 1 month to 10 years 3 months after implantation.

Results

Table 1 summarizes the results of cardiac valve replacement using Wada-Cutter valves according to the type of operation. Early death within 30 days of the operation occurred in 16 patients (13.0%), and the mortality rate tended to be higher among patients with multiple valve replacement than among those with single valve replace-

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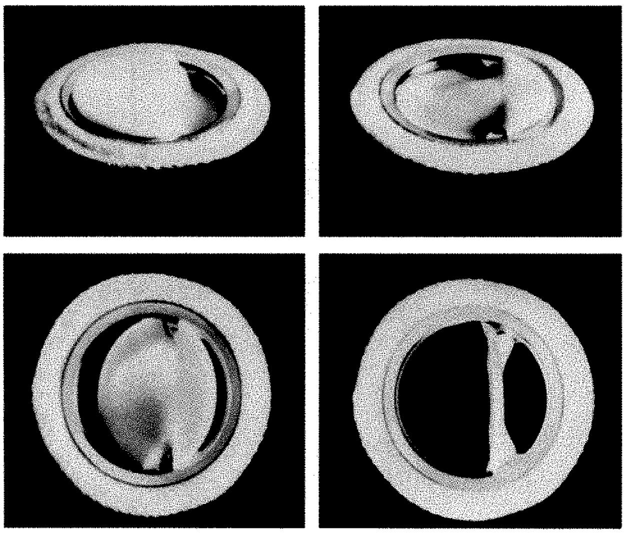

Fig 1. Wada-Cutter prosthesis.

ment. The mortality rate was higher among patients in functional class IV. Low-output syndrome accounted for more than half of the early deaths after operation (Table 2). Late death occurred in 34 (27.4%) patients, and there was no difference in late mortality rate between the single-valve replacement group and multiple-valve replacement group.

The cumulative mortality of the entire group was 40.3%. As shown in Table 3, congestive heart failure, valve thrombosis, endocarditis, and death at reoperation were frequent causes of late death.

Among postoperative valve-related complications, thromboembolism occurred in 4 patients, valve thrombosis in 9, perivalvular leakage in 6, prosthetic valve endocarditis in 5, and mechanical valve failure in 6.

Reoperation for postoperative valve-related complication was performed in 28 patients: 5 with valve thrombosis, 3 with perivalvular leakage, 2 with prosthetic valve endocarditis, 5 with mechanical failure, and 13 as an elective operation.

The procedure performed in the 5 patients with valve thrombosis was valve replacement in 2 and thrombectomy in 3. One of these patients died. Two of 3 patients with perivalvular leakage and all patients with prosthetic valve endocarditis died postoperatively. Of the patients with mechanical failure, 2 of the 3 patients who had occluder embolism [8–11] (of whom 2 successfully underwent suction cleaning of the thrombosed valve without replacement) and 2 patients who had intermittent valve insufficiency due to hinge wear were saved by emergency valve exchange. Prophylactic valve replacement was performed electively in 13 patients with implanted Wada-Cutter valves, resulting in three early deaths.

Table 1. Mortality According to Type of Operation

Operation	No. of Patients	Early Death	Late Death	Cumulative Mortality (%)
AVR	48	6	14	41.7
MVR	56	7	17	42.9
TVR	9	0	0	
AVR + MVR	5	2	1	60.0
MVR + TVR	4	1	1	50.0
AVR + MVR + TVR	2	0	1	50.0
Total	124	16	34	40.3

AVR = aortic valve replacement; MVR = mitral valve replacement; TVR = tricuspid valve replacement.

Table 2. Causes of Early Death

Cause	No. of Patients
Low-output syndrome	10
Valve dehiscence	2
Endocarditis	1
Hemorrhage	1
Arrhythmia	1
Cerebral air embolism	1
Total	16

Comment

The Wada-Cutter valve is a mechanical prosthesis that was first applied to clinical use as a tilting-disc valve on September 15, 1966. This valve had an advantage over the conventional ball valves in that it did not disturb central flow and occupied a smaller intracardiac space, minimizing interference with the left ventricular outflow. This concept of heart valve design subsequently led to development of other tilting disc valves, such as the Björk-Shiley valve [3] and the Lillehei-Kaster valve.

At first, the novel design of the valve appeared promising, and it was used worldwide, especially in the United

Table 3. Causes of Late Death

Cause	No. of Patients
Valve-related death	
Valve thrombosis	4
Cerebral embolism	1
Valve failure	1
Endocarditis	3
Perivalvular leakage	3
Death at reoperation	9
Cardiac-related death	
Congestive heart failure	6
Arrhythmia	1
Other	
Pneumonia	1
Hepatitis	1
Stroke	1
Unknown	3
Total	34

States. Four of the valves were used in the Cooley-Liotta total artificial heart, the first total artificial heart clinically implanted successfully [12]. However, results of long-term follow-up showed increasingly that the valve, implanted without anticoagulant therapy, was not as effective as had been expected in preventing thrombosis, although its self-washing mechanism reduced the frequency of thromboembolism compared with other valves then in use. Moreover, once thrombosis occurred, it was more likely to progress rapidly in tilting-disc valves than ball valves, leading to restriction of the opening of the occluder and severe valve insufficiency. This valve failure was the primary factor responsible for poor long-term results of Wada-Cutter valve implantation.

In vitro fatigue test had indicated that the valve would function for 10 years, but our patients experienced fatal complications such as disc embolization, and intermittent valve insufficiency due to wear of the Teflon occluder hinge [8–11]. Similar complications were also reported by other institutions.

Because of these severe complications and inadequate durability, we abandoned use of the Wada-Cutter valve in the mitral position in 1972 and in the aortic position in 1974. Subsequently, re-replacement was performed in any recipient of this valve who exhibited increased valvular regurgitation sounds or enlargement of the cardiac silhouette on chest x-ray films. Elective re-replacement of the prosthesis also has been performed in patients without any such clinical signs.

The Wada-Cutter valve would have been a better device if pyrolytic carbon, which has a greater antithrombogenic property and is more durable than Teflon, had been used when it became available and if the design of the pivot portion of the valve had been improved.

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Valve Replacement in the Heart Institute, University of Sao Paulo, Brazil

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The initial experience with valve replacement in Brazil was carried out with the mechanical Starr-Edwards prosthesis. In the Hospital das Clinicas in Sao Paulo, 988 Starr-Edwards prostheses were implanted between 1964 and 1971 [1]. The thromboembolism rate in the late postoperative period was 27.4% in the mitral position, and 12% in the aortic (Table 1). After a few cases with homologous and porcine valves preserved in alcohol, clinical use of dura mater with rigid stent commenced in 1971 by Puig and collaborators [2–5]. The dura mater bioprosthesis permitted the maintenance of patients with no anticoagulation and no thromboembolism. The dura mater homograft was used more than 3,000 times in our institute. Subsequently, there was a period in which a dura mater of flexible stent was used, which was followed by an experience with porcine and pericardial xenografts, the latter being developed in the Heart Institute itself (Table 2). Our experience with mechanical valves has been limited, because the philosophy of the Institute is directed to biological valve substitutes.

Experience With Dura Mater Bioprostheses

Dura mater was obtained from cadavers within 14 hours after death. Specimens with infection, degenerative disease, or cancer must be ruled out. The scalp is incised and pulled forward. The skull, meninges, and brain are sawed 1 cm above the glabella and the mastoid. The brain is removed and the dura mater is detached from the skull. The superior sagittal sinus is opened and the dura mater is washed in running water for one hour. Immediately afterward, dura mater is fixed and preserved in 90% glycerol for at least 12 days at room temperature. The preparation of the valve is carried out aseptically in the operating theater. The dura mater is rehydrated in saline solution for about five minutes. The valve is composed of three leaflets sutured to a Dacron velour–covered stainless-steel frame. Each leaflet is tailored in the shape of steel templates of different sizes. The leaflets must have similar thickness and flexibility.

The leaflets take the shape of a set of casting molds. They are sutured to the Dacron velour–covered frame by a continuous row. A fragment of the dura mater is secured for bacteriological cultures.

From 1971 to 1980, 2,647 patients received bioprostheses of dura mater with rigid stent. The mitral valve was replaced in 1,218 patients (46.2%). The aortic valve was replaced in 1,075 patients (40.61%). Tricuspid replacement was necessary in 49 patients (1.85%). The pulmonary valve was replaced in 5 patients with congenital heart disease (0.18%). Multiple valve replacement was performed in a group of 300 patients (11.34%). From 1980 to 1982, 180 patients received dura mater valves with flexible stent.

We believe that it is important to analyze in greater detail the 10-year follow-up study of Zerbini and colleagues [6]. From 1971 to 1973, 243 consecutive patients were operated on, 147 (60.49%) requiring mitral replacement, 88 (36.22%) aortic replacement, and 8 (3.29%) tricuspid replacement. A total of 25 (10.28%) patients were lost to follow-up. The age of the patients varied from 6 to 67 years, with a mean age of 34.1 years; 50.61% were male and 49.38% female. Aortic replacement was more frequent in male patients (73.86%) and mitral replacement in female patients (61.20%). After mitral replacement, the immediate mortality in the series of 147 patients was 12.92% and late mortality was 19.29%. Mild or questionable thromboembolic episodes were observed in 1 patient (0.68%) during the immediate postoperative period, and in 1 patient (0.8%) during the late postoperative period. Valve dysfunction was observed in 10 patients during the immediate postoperative period, including 8 with mild systolic murmurs and 2 with perivalvular leak. During the late postoperative period, 14 patients had mild systolic murmur, 14 suffered ruptured cusps, and 3 had calcification of the valve leaflets.

Nineteen reoperations were performed in the following 10 years. Two patients had perivalvular leakage and were reoperated on at 5 and 19 months. Rupture of the cusps was observed in 14 patients who underwent valve replacement in the period from 35 to 108 months after the first operation. Calcification of the cusps required reoperations in 3 patients in the period from 60 to 90 months after the first operation. The low incidence of calcification in this initial series is explained by the small number of children.

In the 10-year postoperative period, 61.6% of the patients were asymptomatic (New York Heart Association [NYHA] functional class I). In the actuarial analysis of reoperation of the patients who underwent mitral valve replacement, patients free of valve dysfunction comprised 95% of the survivors 6 years after valve replacement; 86.5% after 7 years; and 53% 10 years after operation. In aortic replacement (88 patients), the immediate mortality was 11.36%, and the late mortality was 16.17%.

Fungal endocarditis was observed in 1 patient (1.47%) during the late postoperative period. Bacterial endocardi-

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Table 1. Starr-Edwards Valve: Initial Experience

Position	No. of Patients	Immediate Mortality (%)	Late Mortality (%)	Thrombo-embolism (%)
Mitral	459	11.5	5.2	27.4
Aortic	372	13.9	3.7	12
Tricuspid	13	15.4	7.7	—
Multiple	154	19.5	8.4	18.8
Total	998			

tis occurred during the immediate postoperative period in 1 patient (1.13%), and in 7 patients (7.95%) during the late postoperative period. There was one late thromboembolic episode (1.4%). Valve dysfunction was observed during the immediate postoperative period in 4 patients, including 2 with mild diastolic murmur and 2 with perivalvular leakage. During the late postoperative period, 7 patients had mild diastolic murmur and 32 had ruptured valves.

In the 10 years' experience, 37 reoperations were performed. Rupture of the cusps was observed in 32 replaced valves resected from patients reoperated on in the period between 38 and 94 months after operation; in this group, two deaths occurred (5.4%).

In the 10-year postoperative period 75% of the patients were asymptomatic (NYHA functional class I). In the actuarial analysis of reoperation of the patients who underwent aortic valve replacement, patients free of valve dysfunction comprised 73% of the survivors 5 years after valve replacement; 60% after 6 years; 53.84% after 7 years; and 24% 10 years after operation.

From this report we conclude that the actuarial survival after mitral and aortic valve replacement by dura mater homograft is acceptable. However, the percentage of survivors free of valve dysfunction shows an appreciable decrease 7 years after valve implantation. The patients were able to reach several years of benefit without thromboembolism and without the inconvenience of anticoagulants. Valve dysfunction was gradual and allowed time to reoperate with low mortality.

Table 2. Bioprosthesis Experience

Period	Type	No. of Patients
Nov 1966–June 1967	Homologous: aortic position (formaldehyde 4%)	50
Dec 1968–Sep 1969	Porcine (alcohol 70%, glycerol)	20
1971–1980	Dura mater (rigid stent)	2,647
1978–1982	Dura mater (flexible stent)	180
1982–1987	Porcine xenograft (glutaraldehyde-preserved)	461
1982–1984	Pericardial xenograft (glutaraldehyde, 0.56%; formaldehyde, 4%; high profile)	273
1984–1987	Pericardial xenograft (glutaraldehyde, 0.56%; formaldehyde, 4%; low profile)	561
Total		4,192

We know that bioprostheses are neither hemolytic nor thrombogenic, but the greatest problem is related to their durability. A histological study of the tissue utilized, and of the bioprostheses that were removed, is undoubtedly very important.

Structural changes of dura mater in working valves in patients were studied by Allen and associates [7–9]. Histological investigations with light microscopy of recovered glycerine-treated dura mater revealed preservation of collagen fibers showing normal aspect in both longitudinal and cross-section. They retain good staining characteristics and show no evidence of host cell infiltration. However, study of subcellular structures of the dura valve allograft showed surface and internal alterations.

Whereas scanning electron microscopy provides valuable information on phenomena occurring on the surface of the prosthetic devices, transmission electron microscopy detects changes that take place both on the surface and within the substance of the implanted prosthesis. In addition, x-ray microanalysis permits identification of the structures under examination, furnishing precious information on the chemical composition, suggesting a remodeling process when recovered valvular leaflets are compared with controls.

The alterations observed in the surface of the glycerin-treated dura mater of the valves recovered from patients were similar to those described by Ferrans and colleagues [10] for glutaraldehyde-treated porcine heterografts. However, significant differences were observed between the cells found within the glycerin-treated dura mater allografts and glutaraldehyde-treated porcine heterografts.

Electron microscopy of the connective tissue of implanted dura mater leaflets surgically recovered from patients over a period of 23 to 73 months after implantation revealed interwoven bundles of collagen fibers, fibroblasts, and macrophages imbedded in a translucent ground substance. Dense orcein-positive material was observed in strands dispersed throughout the remodeling areas, and often in close juxtaposition to the fibroblasts. Microfilaments were also observed in distinct layers or bands along the plasmalemma of the fibroblasts. Macrophages were observed within the fibrin of the valvular surface and within the connective tissue matrix of the valve leaflets. In areas of remodeling, there was evidence of morphological degeneration of the connective tissue fibers (collagen), characterized by an absence of cells (cellular degeneration) and lipid deposition, in addition to evidence of collagen synthesis.

Such findings indicate that the bioprosthetic dura mater valves are not passive structures but active in the process of degeneration and remodeling on the surface, in continuous contact with the bloodstream, and in the substance.

We conclude that the changes observed at the subcellular level in the glycerin-treated dura mater surgically

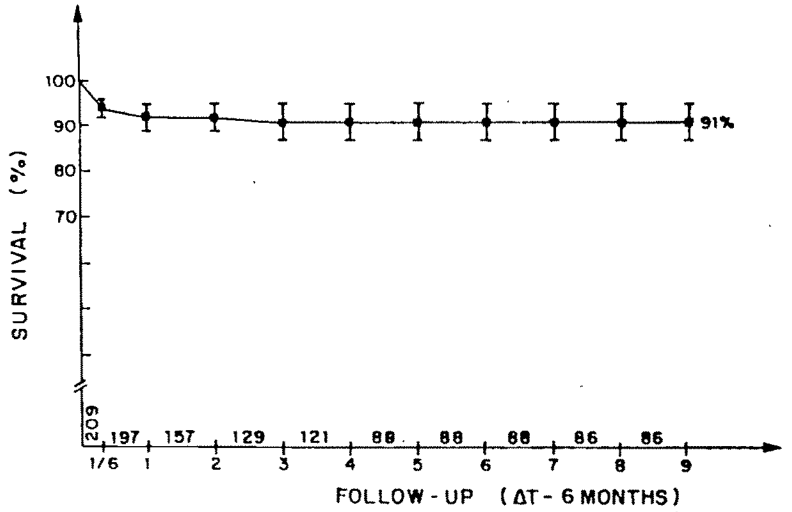

Fig 1. Actuarial survival after isolated aortic valve replacement with pericardial xenografts (Jan 1984 to June 1988).

recovered from patients probably interfere with its limited durability.

Experience With Pericardial Xenografts

We have been utilizing pericardial xenografts fixed in glutaraldehyde (0.5%) and preserved in formaldehyde (0.56%) and preserved in formaldehyde (4%) since 1982, a low-profile flexible stent being presently used because with the high-profile stent, some cases of left ventricular outflow obstruction were observed. Up to 1987 a total of 987 prostheses were inserted in 834 patients with a minimum age of 7 years and a maximum of 79 years (average age, 41 years); 304 valves were high profile and 683, low profile. The average follow-up period was 26.8 months [11].

The immediate mortality of patients in whom high-profile pericardial xenograft prostheses were implanted in the aortic and mitral positions was, respectively, 4.7% and 7%; for the low-profile pericardial xenograft bioprostheses, the mortality was 2.3% and 9.3%, respectively.

In the late postoperative period the patients with high-profile prostheses had the following complications: calcification, 0.33%/patient-year; ruptured cusp, 0.33%/patient-year; and endocarditis, 0.13%/patient-year. In patients with low-profile prostheses the complication rates were: calcification, 0.2%/patient-year; ruptured cusp, 0.05%/patient-year; and endocarditis, 0.10%/patient-year.

The actuarial analysis for patients with high-profile aortic prostheses shows 94% survival in 13 semesters (Jan 1982 through June 1988); survival is 84% for the patients with high-profile mitral prostheses. For those with low-profile prostheses the actuarial analysis in 9 semesters (Jan 1984 through June 1988) showed 91% survival for patients with aortic prostheses (Fig 1) and 84% for patients with mitral prostheses (Fig 2). Obviously, the period of evolution is still too short for conclusions to be reached. Our results with the porcine bioprostheses are similar, showing 82% survival free of complications in an actuarial analysis after 5 years.

To conclude, we have been informed that the dura mater bioprosthesis is still used in Russia and India, and that it is also the bioprosthesis used in artificial heart development at the Cleveland Clinic.

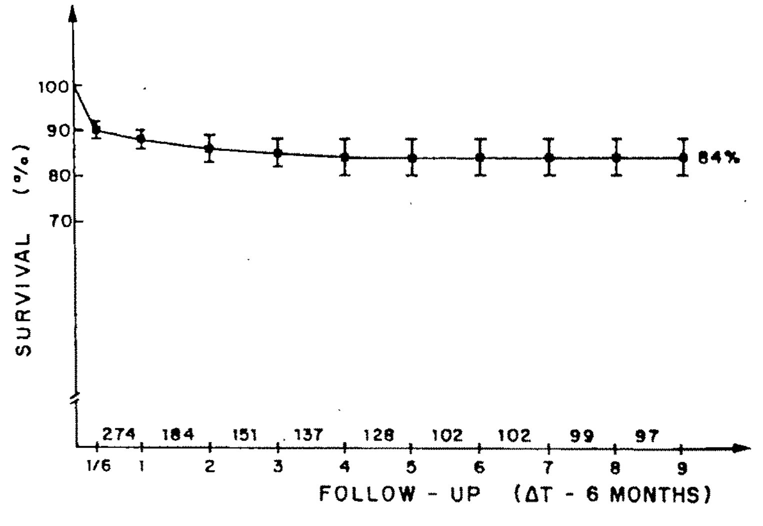

Fig 2. Actuarial survival after isolated mitral valve replacement with pericardial xenografts (Jan 1984 to June 1988).

Results with dura mater are not very different from those of porcine and pericardial bioprostheses. In the aortic position, despite ruptured cusps, the incidence of endocarditis and calcification was low. Many patients have shown a satisfactory evolution beyond 10 years. Why has this study been interrupted? Because human material is harder to obtain and the fixation with glutaraldehyde, even in low concentrations, has not been achieved.

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The Development of the Cross-Jones Caged-Lens Prosthesis

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After a variety of valves had been tested since 1958, work on the low-profile lens valve was begun in May 1964, and the first valve was implanted on January 5, 1965. This first patient lived 15 years, dying of causes not related to the valve. The low-profile caged-lens valve consisted of a titanium ring, a silicone rubber lens-shaped disc, and a woven Teflon fixation flange. The free-floating lenticular disc was held in position over the valve orifice by a cage formed by three legs machined from a solid piece of titanium. The silicone rubber lens was reinforced with a thin titanium ring molded in place within the lens. The weight was reduced by molding an air pocket within the silicone rubber lens. Lens weight was substantially less than that of a silicone rubber ball in a valve of the same size. This design resulted in a lightweight, low-profile valve with rapid opening and closing action, as well as adequate primary and secondary orifices for unhampered blood flow. The small profile of the valve also ensured an adequate tertiary orifice. With the exception of reports of ball variance, the early mechanical valves functioned satisfactorily over long periods of time. The early and persistent problem was fibrin clot or pannus formation at the cloth–metal interface, causing embolization and valve obstruction. A possible solution to this problem seemed to be the elimination of the cloth–metal interface by a number of subsequent modifications.

Covered Rim Valve

In this valve, the entire rim of the valve was covered with Dacron or polypropylene mesh to promote tissue ingrowth. Although tissue ingrowth did occur, serious problems remained. There was still fibrin clot formation at the base of the legs where they emerged from the cloth covering, sometimes to the extent that it interfered with the function of the disc. In addition, there was incomplete healing of the tissues over the rim. Bruised areas developed from the poppet striking the rim, resulting in ulceration and fibrin accumulation. In some instances, there was abrasion of the disc by the cloth that remained uncovered by tissue, resulting in abnormal disc wear. Finally, there could be excessive connective tissue formation around the rim, resulting in a narrowed valve orifice and valve stenosis. To solve these problems, a thin metal rim was left in the orifice for the poppet to close against. This eliminated the bruising and ulceration seen in the totally covered rim and, theoretically, because the rim was in a high-flow area, fibrin clot formation was diminished or eliminated at the cloth–metal interface. Following the same reasoning, Starr left small exposed metal pegs for the ball to close against on his cloth-covered rim valve.

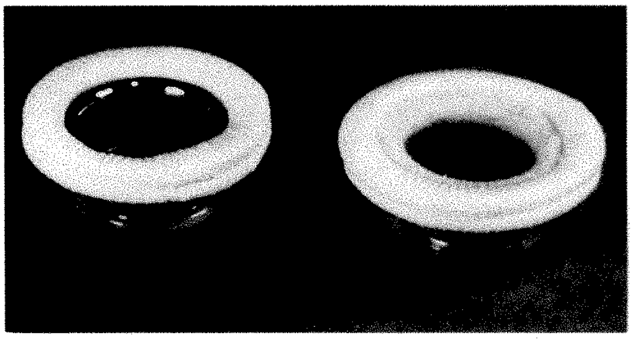

Fig 1. Cross-Jones lens mitral valve: (Left) basic rim model; (Right) covered rim model.

Total Cloth-Covered Valve

To eliminate fibrin formation at the junction of the cloth-covered rim and the legs, the entire valve was covered with Dacron mesh. This proved a disaster in the laboratory and, subsequently, clinically. Deep grooves were worn in the disc and the cloth was worn off the legs. To avoid abrasion of the lens, the inside of the legs was then left bare but, although the lens was protected, there was continued clotting around the legs. Starr's solution to this problem was the track valve design in which a thin metal strip was placed on the inside of the cage for the ball to travel on.

Screen Lens Valve

This valve was of a somewhat ingenius design made from stainless-steel screening. The open orifices of the screen allowed tissue ingrowth through the interstices for firm encapsulation by the surrounding tissues. The valve was surprisingly well-accepted by the tissues and there was minimal to no fibrin clot formation. This valve was never developed for clinical use, but functioned well in dogs and calves for periods up to 6 months. The basic concept has been used at the tips of pacemaker electrodes and in the manufacture of vessel stents placed after transluminal dilation of the coronary arteries.

Disc Modification

In an attempt to eliminate disc wear by the cloth-covered legs, a titanium lens was substituted for the more abra-

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sion-prone silicone rubber disc. Although the disc was spared, an unexpected new problem presented itself. After only 6 weeks there was serious wear of the legs by the titanium disc. In an attempt to avoid such wear, the legs were covered with Teflon tubing, but wear of the tubing (and then wear of the legs by the disc) was not avoided. At the time of these observations, there were other valves already in clinical use that used the combination of a titanium cage and poppet. Our conclusion from the above studies was that, from the practical standpoint, the best solution was to cover the valve rim with polypropylene mesh or Dacron and leave the legs bare. Such a valve was introduced clinically. It had rather limited use, but suffice it to say the same problems persisted clinically as in the experimental animal.

Full-Orifice Double-Cage Valve (Cutter-Smeloff Type)

The final modification of the low-profile caged-lens valve was to develop a full-orifice double-cage valve of the Cutter-Smeloff design. Whereas this valve functioned well in dogs, it was not used clinically by us, but a similar design was used by Cooley as the Cooley-Cutter low-profile valve.

Three years' early experience with 224 Cross-Jones valves implanted in the mitral or tricuspid area in 214 patients indicated that long-term durability and function of the valve were satisfactory. The incidence of fatal clotting complications with the 224 valves was 3.5%; the incidence of nonfatal nonthromboembolic problems was 8.7% with 196 valves in place for 1 month or more. Although it was expected that covering the valve rim with Dacron mesh would decrease this incidence, it did not prove to be true. In a recent report [1] of 75 Cross-Jones valves examined after being in action for two days to 10 years, the only problems arose with valves with covered rims. As in the experimental animal, the covered rims first became encapsulated by a connective tissue layer and then became ulcerated until, finally, the polyester and connective tissue coverings cracked and curved up, resulting in a ragged bed. This in turn produced substantial peripheral wear of the discs causing valve insufficiency and, in several instances, actual escape of the discs from the cage because of excessive wear. In 19 uncovered prostheses, there was no sign of serious alteration. The discs were not deteriorated or worn, and the valve beds were smooth up to 10 years after insertion.

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The Medtronic Hall Heart Valve: Background, Latest Results, and Future Work

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Background

Norway, with just over four million people, has the smallest population of the Scandinavian countries. Rikshospitalet, the Federal University Hospital, is located in Oslo. Open heart surgery began there in 1958 and implantation of valve prostheses in 1964. During the 1960s, ball valves were predominantly used. This new technique saved the lives of many Norwegians, but cases of thromboses and embolization indicated that ball valves were not the final answer to the problem. In addition, the hemodynamic performance of these valves in small aortic ostia was less than satisfactory. In the mitral position, ball valves required space in the left ventricle and could present a hindrance in the outflow tract.

The introduction of the tilting-disc valve around 1970 attracted our interest because of its low profile and better hemodynamic performance. The new material of the occluder, pyrolytic carbon, seemed to be a better choice than plastic, which could fail for a variety of reasons, and the principle of a rotating disc, we felt, could eliminate the wear problem of the Wada-Cutter disc valve.

We were first offered the Björk-Shiley valve, and we used it for a few months before the Lillehei-Kaster valve was offered to us for preclinical trials. Which one of the two valves was preferred? The larger opening angle of the Lillehei-Kaster valve, I supposed, must result in less resistance to forward flow than was the case with the Björk-Shiley valve. On the other hand, the nonocclusive principle of the Björk-Shiley valve offered a greater flow area within the valve ring.

A problem of a different nature was the personal relationship I had with the surgeons Björk and Lillehei. Lillehei has Norwegian roots, and Björk was a friend in the neighborhood. These circumstances inspired me to start a randomized study of the two disc valves, which provided these results:

1. The nonoverlapping, or full-orifice, principle of the Björk-Shiley valve was better than the overlapping disc in the Lillehei-Kaster valve. In theory, the Lillehei-Kaster 80-degree valve should have less resistance to flow than the Björk-Shiley 60-degree valve because of the larger opening angle. But roentgenographic studies showed that the in vivo opening angle was actually less than 60 degrees in the Lillehei-Kaster valve.
2. The Lillehei-Kaster valve caused more hemolysis.
3. The problem of mechanical failures seemed to have been solved, but there was still an unacceptable number of cases of valve thromboses among the disc valve patients. Autopsies revealed that these thromboses were located on the outflow side of the valve and around the smaller opening. An important finding was that the postoperative contrast studies showed a zone of stagnant flow behind the disc in the aortic position. A weak point of the Björk-Shiley valve was that the edge of the disc touched the valve ring in the open position. Thrombotic material was regularly found at this critical point in cases of valve thrombosis.

The results of this randomized study encouraged me to modify the tilting-disc configuration to achieve a hybrid of the two valves. We preferred the nonocclusive principle of the Björk-Shiley valve, in order to have the largest possible orifice area. We utilized three additional design principles: (1) to reduce the stagnant flow behind the disc and reduce resistance to forward flow, the valve had to open clinically to more than 60 degrees; (2) to establish a clearance between the edge of the disc and the orifice housing and allow the blood to wash away the platelet aggregates at the "critical" point mentioned earlier, we introduced a sliding movement of the disc when it opened; and (3) to increase the small opening, we moved the tilting axis further toward the center of the valve ring, compared with the previous two designs.

But all of these changes might delay the closure of the disc and thereby establish a leak. How far could we go without creating an incompetent valve? It was obvious that a pulse-duplicator had to be available and several prototypes for testing as well.

I lacked the funding to undertake such a costly endeavor, but a friend of mine named Arne Woien got things started. He is a physicist and a businessman with sufficient funding to support worthwhile projects. Also of decisive importance was the inclusion in the team of Robert Kaster, who had been instrumental in the construction of the Lillehei-Kaster valve. All three of us contributed equally to the design of the Hall-Kaster valve, which is now called the Medtronic Hall valve (Fig 1). The design of the standard valve has been unchanged since the first clinical implantation. This design incorporated features to address all three problems: (1) the valve opened to 75 degrees (70 degrees in the mitral position); (2) a sliding movement at the end of opening and the start of closing, achieved by having a disparity in size between the diameters of the end of the rod guide and the hole in the disc, allowed the disc to move clear of the orifice; and

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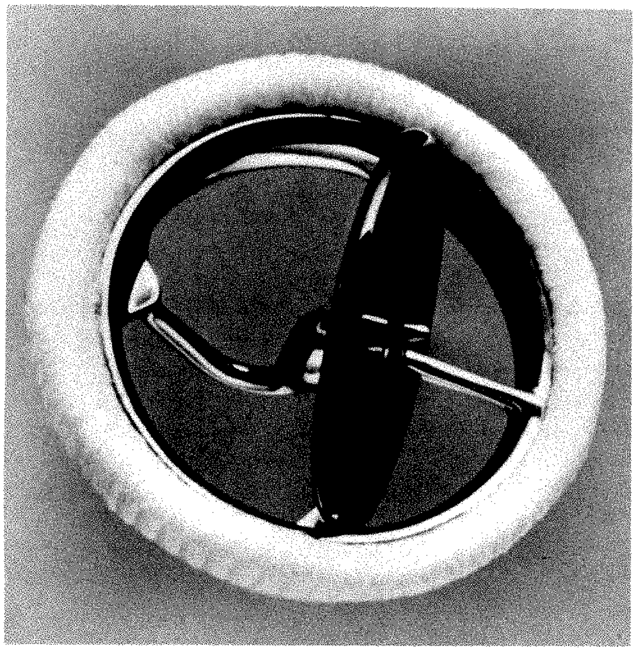

Fig 1. Medtronic Hall heart valve, originally called the Hall-Kaster valve.

(3) the disc pivots were located more centrally in the orifice, creating a proportionally larger minor orifice.

In vitro comparisons showed that the hemodynamics of the new valve compared favorably with those of the Björk-Shiley and Lillehei-Kaster valves: the valve exhibited lower gradients and higher cardiac output with increasing left ventricular pressure.

The first implantation was performed in June 1977. Intraoperative studies and recatheterization studies 3 months after operation showed that the Medtronic Hall valve had lower resistance to forward flow compared with the previous tilting-disc designs. The 21-mm aortic valve had a mean peak-to-peak gradient of 12 mm Hg at rest, which increased to 15 mm Hg at work, and the 27-mm mitral valve had a gradient of 3 mm Hg at rest [1].

Latest Results

The worldwide experience is now approaching 100,000 implants, and extends beyond 11 years. It is exceptionally satisfying to see that the concepts we incorporated into a design so many years ago have resulted in clinical benefits to so many patients.

The most recent results from our institution were presented at the latest meeting of the American Heart Association [2]. This review of our entire series of over 1,100 patients spanned 10 years and 5,000 patient-years. Our standard follow-up of these patients included annual questionnaires, as well as close contact with local physicians and hospitals whenever necessary. We demonstrated an incidence of thromboembolism of 1.3% per year in both the aortic and mitral positions, and 1.8% for double-valve replacement. Thrombosis rates were 0.1% per year in both aortic and mitral positions, and 0.2% per year for double valve replacement. These rates of thromboembolic complications were shown to compare favorably with those in recent reports of large series with other valve models, supporting the goal that our design changes were intended to produce.

In addition to the previously demonstrated excellent hemodynamic performance of the Medtronic Hall valve, our 10-year review demonstrated that long-term performance is characterized by low risks of thromboembolism and thrombosis and no structural failure. We believe that we have optimized the tilting-disc design and achieved a substantial improvement in results compared with the previous tilting-disc designs.

Future Work

Personally, I believe that the problem of mechanical reliability has been solved. As for hemodynamics, I believe that the function of the present mechanical valve is fully satisfactory for clinical purposes, even in the smaller sizes.

Although the remaining problems of thrombosis and thromboembolism, provided optimal anticoagulation is achieved, affect a relatively small proportion of the patients, these problems still need to be resolved in even the best mechanical valves. It is astonishing how little attention has been paid to research concerning the sewing ring. Of the 5 cases of valve thrombosis we have seen, all have had some connection with the sewing ring. The high shear rate and polished surfaces in the central stream have never initiated thromboses. I am convinced that we will see improvements and in time will solve the remaining problem of thrombotic complications.

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Carbon in Prosthetic Heart Valves

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Pyrolytic carbon of the sort developed for use in the generation of nuclear power was first used clinically in a prosthetic heart valve in 1969 [1]. Its emergence as a material showing promise for use in constructing prosthetic heart valves was preceded by a development that can be likened to a confounding riddle, with many-faceted clues, that persistently evaded solution.

The development stems from a report in 1925 by Abramson [2] that cellular and molecular elements of blood carry a negative charge. This observation, together with the report by Sawyer and Pate [3] that the inner lining of blood vessels was negatively charged with respect to the outer surface, led Gott and associates [4] to reason that if they put a negative charge on a prosthetic valve, it would not clot. To test the idea, specimens coated with a conducting carbon paint and connected to a battery were implanted in canine venae cavae. Indeed, when a specimen was charged positively, it clotted; when it was negatively charged, it did not clot. In one experiment, however, the electrical lead broke and the specimen with no charge did not clot.

Although carbon-pigmented paint appeared to be thromboresistant, this was not really the case. After careful sterilization studies of the carbon paint, Gott and associates [4] found that the paint was only thromboresistant when it was soaked first in benzalkonium chloride and then in heparin solutions. There appeared to be a chemical bond between heparin and benzalkonium ions and between benzalkonium and carbon.

A chance reading of a report by Gott and co-workers [5] in 1965 led to a collaboration between Gott's medical research team and our group, which was developing carbon materials for use in nuclear reactors at General Atomic Company (San Diego, CA). Results from these collaborative studies (funded by the National Institutes of Health's Artificial Heart Program) showed that the conductive carbon paint per se was not thromboresistant. Rather, it was shown to possess a surface porosity in which benzalkonium and heparin molecules reacted during the preimplantation treatment to form a gelatinous benzalkonium/heparin complex that, when placed in blood, slowly eluted heparin and caused the thromboresistance.

A surprising finding was that the polished surface of isotropic pyrolytic carbon, in spite of its inability to bind either benzalkonium or heparin, was inherently thromboresistant. This led to the development of a pyrolytic carbon, called Pyrolite carbon, that was first used clinically in the DeBakey aortic prosthesis and then in the Beall mitral, Lillehei-Kaster, Björk-Shiley, and other prostheses that followed.

The use of pyrolytic carbon in the St. Jude valve represents an important advance, because that valve was the first with fixed pivots to become clinically successful. The valve's success was due as much to the remarkable wear-resistance of carbon rubbing on carbon as it was to its biocompatibility, and led to the all-carbon Duromedics and CarboMedics valves—and a number of others that are still under development [6].

During the 19 years since the first clinical use in 1969, more than 1.4 million carbon components have been produced for use in about 1 million valves. This usage is estimated to represent an experience of over 5 million patient-years. The acceptance of pyrolytic carbon is due to the fact that it possesses a combination of biocompatibility and durability that is unmatched by any other material. Even so, the development continues; the ideal prosthetic valve still does not exist.

Although the hemodynamics of tissue valves have been improved dramatically, there remain serious deficiencies in durability due to material fatigue that is accelerated by calcification. Hence, use of mechanical valves is currently favored. Improvements in tissue valves will be difficult, and, because of the long-term testing required to prove a result, will likely be slow to come. Mechanical valves, on the other hand, are sufficiently durable but lack thromboresistance, so that anticoagulation therapy is required, with possible attendant bleeding problems.

The thrombogenicity of mechanical valves is thought to be due primarily to inadequate hemodynamics; eg, excessive turbulence and high shear stresses during forward flow and/or imprecisely designed leakage that is allowed back through the pivot mechanism for washing.

The washing of the pivots of the Duromedics valve is an example that illustrates the concept of washing by backflow leakage. In the closed position, the leaflets of this valve rest on seating lips so that there is no contact in the hinge mechanisms and clear, smooth pathways exist for leakage and concomitant washing. When the valve is closed and the pressure differential across the valve peaks to its maximum, backflow is supposed to scour the pivots, eliminating stases and, at the same time, avoiding jetting that can lead to hemolysis or other manifestations of blood trauma that can cause clotting [7].

There is also opportunity for improvements in the quality of forward flow through mechanical valves. Both the St. Jude and the CarboMedics valves use flat leaflets; the leaflets of the Duromedics valve are curved about axes perpendicular to the pivot axes, so that all three valves project a straight profile inclined to the valve axis when open and viewed parallel to the pivot axis. It is likely that

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improvements in the quality of flow can be realized if the leaflets in the open position are optimally curved about axes that are perpendicular to the valve axis, so that flow separation is surpressed. Accordingly, bileaflet valves with improved micro and macro flow characteristics that are less traumatic to blood might eliminate or reduce the need for anticoagulation therapy.

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The Ball Valve Experience Over Three Decades

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It was more than 30 years ago that a retired electrical engineer named Lowell Edwards came to the office of Dr Albert Starr at what is now The Oregon Health Sciences University in Portland, Oregon, and proposed that together they build an artificial heart. Mr Edwards was advised that this plan was a little ambitious at that time, but that a prosthetic heart valve would be a more attainable goal. Over the succeeding years the collaboration of these two men at The Oregon Health Sciences University led to the design and methodical testing of the Starr-Edwards Silastic ball prosthesis. This work was eventually rewarded by the first successful human mitral valve replacement performed on September 21, 1960, in a 52-year-old man with calcific mitral stenosis [1].

The very earliest prosthetic configuration they tested had a cloth sewing ring for fixation and a rigid Teflon body to maintain its shape. The closing mechanism was composed of a central Silastic bileaflet device. Several different types of leaflet configurations were tested in dogs, and all of these thrombosed within a matter of days.

Two of the major problems addressed during the early years of experimental work were that of thrombosis and that of how to affix the device to living tissue. This latter obstacle had to be resolved so as to provide for a permanent implant without perivalvular leak. For this reason the sewing ring was modified to a multilayer structure to provide for compressibility and avoid annular ulceration. With regard to valve thrombosis, it was reasoned that this complication might best be avoided if some discontinuity could be provided between the prosthetic orifice and the closing mechanism. This was the case for a ball valve. Nevertheless, in the dog, the problem of early thrombosis was difficult to solve. Thrombus invariably started at the zone of injured endocardium at the tissue–prosthesis interface. This material would then propagate in a centripetal fashion and obstruct the central orifice of the valve, usually over a period of about 3 weeks.

Valve thrombosis was eventually circumvented with the use of a peripheral Silastic shield mounted on the valve [2]. This shield could be retracted out of the way during implantation and then laid down to cover the zone of injured endocardium circumferentially. The shielded ball valve allowed for 80% long-term survival when implanted in the mitral position in dogs. With this long-term survival it was then possible to demonstrate actual healing at the cloth-tissue interface, and it was seen that this encapsulation stopped at the junction between cloth and metal.

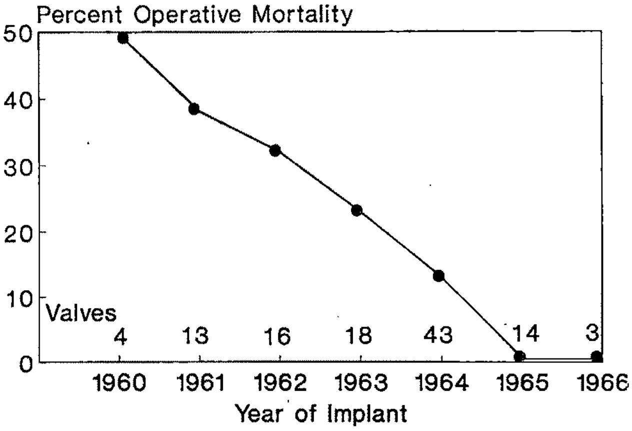

Fig 1. Operative mortality by implant year for Model 6000.

The first commercially available ball valves were composed of four stellite struts joined at the apex of the cage and had a woven multilayer sewing ring and a radiolucent poppet. These valves were used between 1960 and 1965.

These early years of clinical valve replacement were instructive in a number of ways. First, the surgical procedure was mastered. This is demonstrated by the rather steep "learning curve" beginning with 50% operative mortality for the 4 cases done in 1960 and progressing to very acceptable levels of operative risk 5 years later (Fig 1).

It was also learned that, although patient survival was distinctly improved in comparison with the natural history of the disease, there was nevertheless a continuous attrition of patients with time. The long-term survival for these early patients approximated 80%, 60%, 40%, and 20% at 5, 10, 15, and 20 years postoperatively [3]. But it was also determined by regression analysis that long-term survival was related to intrinsic patient pre-

Table 1. Thromboembolism Rates of Mechanical Mitral Valves: 1983–1987

Model	Reports	Patient-Years	Thrombo-embolism Rate
Starr–Edwards	9	19,949	4.4
Björk–Shiley	9	6,188	3.3
St. Jude	11	4,104	1.6
Medtronic Hall	7	4,053	2.6
Omniscience	5	1,017	2.8

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Table 2. Thromboembolism Rates of Mechanical Aortic Valves: 1983–1987

Model	Reports	Patient-Years	Thromboembolism Rate
Starr–Edwards	7	21,760	2.3
Björk–Shiley	9	7,753	1.9
St. Jude	11	5,418	1.4
Medtronic Hall	6	6,570	1.8
Omniscience	4	753	2.7

operative characteristics such as age, cardiac index, previous heart operation, and associated aortic disease rather than the prosthesis itself [4]. The Model 6000 was modified to extend the cloth covering toward the orifice and impregnate the ball with barium sulfate to make it radiopaque. The result was the Model 6120, which has been available continuously without change since 1965. Because of the successful results with the mitral design, an aortic model with three struts was developed, and similar modifications resulted in the current Model 1260, which was introduced in 1968. While the Models 6120 and 1260 continued to be used worldwide, an attempt to reduce thromboembolism in the mid-1960s led to the development of a totally cloth-covered series of valves and the so-called "track valves," which all had hollow stellite poppets rather than a Silastic ball.

In the late 1960s and early 1970s, while the cloth-covered models were being explored, however, data continued to accumulate on the Models 6120 and 1260 Silastic ball valves. They showed that the cloth-covered valves offered no advantage and that they had an acoustic disadvantage. Furthermore, with cloth wear there was increased hemolysis. For these reasons, the cloth-covered valves were abandoned in 1982.

In the many years since the introduction of the Starr-Edwards valve, many other mechanical prostheses have been developed and marketed. Quite recently we have had the opportunity of pooling the data from a number of reports in the literature concerning the Starr-Edwards valve and a number of other popular mechanical valves [5]. Recognizing the pitfalls of statistical comparison of prosthetic valves, we were struck by the wide scatter of reported thromboembolic and thrombotic rates for any given valve in different series. Pooling these results to provide overall averages allows the comparisons seen in Tables 1 and 2 and Figures 2 and 3. A striking difference is seen in the amount of follow-up available for the Starr–Edwards valve when compared with the more recently developed mechanical valves. Thromboembolic rates for all mechanical valves are of comparable magnitude but may be somewhat less for more recently developed prostheses, though this remains to be confirmed by extended follow-up and reporting. Comparison of pooled thrombosis rates for these mechanical valves shows that the Starr-Edwards valve compares quite favorably with the other mechanical prostheses; in particular, this complication was definitely greater for the tilting disc valves. Finally, when mechanical structural failure is considered, there remain no reported incidents of this catastrophic complication with the Starr-Edwards Silastic ball valve. For these reasons the Starr-Edwards valve remains our mechanical valve of choice.

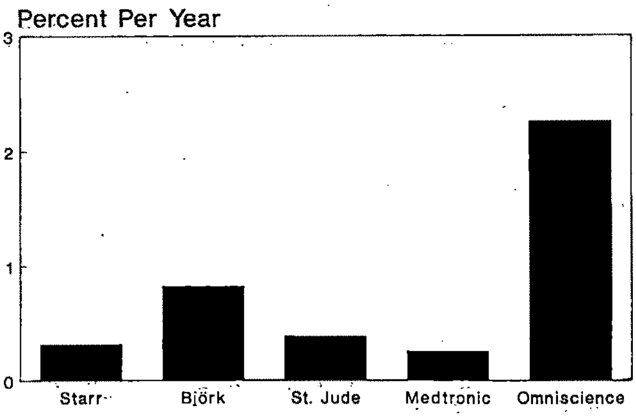

Fig 2. Pooled thrombosis rates for mechanical mitral valves: 1983–1987.

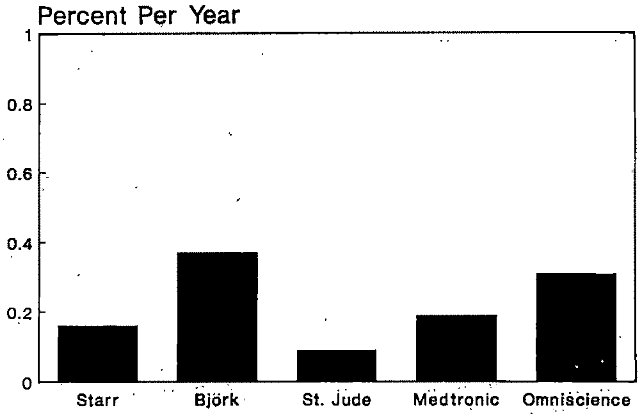

Fig 3. Pooled thrombosis rates for mechanical aortic valves: 1983–1987.

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"It Will Never Work!"—The St. Jude Valve

Manuel A. Villafana

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In March 1976 I was in Tokyo, Japan, meeting with several physicians talking about the possibility of developing a new valve. Our friend Juro Wada was one of those physicians, and we had just finished developing the first lithium-powered pacemaker (Cardiac Pacemakers, Inc). We had no previous experience in heart valves, and therefore no previous myopia. We received many comments.

> "Manny, rheumatic fever is being eradicated—there is no market."
> "The market is insignificant—only $40 million." (Today it's over $200 million.)
> Our friend, Dr Friedberg said, "All you're doing is changing one bad disease for another bad disease."
> "You'll never be able to raise the capital to start this project."

But one major thought did remain in my mind, and that was the comment of Dr Victor Parsonnet, who said to me, "Manny, what we need, more than anything else, is a good heart valve."

So we proceeded. Our first conflict was the name of the company. I called on my good friend Dr H. David Friedberg and asked him if he, being of the Jewish religion, would be offended by a company named "St. Jude Medical, Inc." His comment to me was, "Manny, St. Jude was a fine Jewish boy."

We began with a design that was introduced to us by an engineer, Chris Possis, which was a bileaflet design. However, we immediately had to abandon it as that design would not work at all. It is important to remember that we had no previous experience in heart valves, so we were unable to determine if a design that was handed to us would have any chance at all. But we did make one decision, a decision that I'm sure is surprising to the medical profession: we decided that the valve would be all carbon, because of carbon's nonthrombogenic properties, and bileaflet, because this would make a marketing impact. That is to say, we would make a valve different than anything else. Surprisingly, this was not a scientific decision, although later it proved to be the best scientific decision we ever made. We began trying everything—we even went home, unrolled the toilet paper, and kept the cardboard tubes so that we could cut them up and use them to make different designs. We tried different designs in our bathtubs at home; we made clay models. Our nonvalve engineer, the gadgeteer Don Hanson, with the input of our other officers (Bill Palmquist and Peter Gombrich), devised the design that we would eventually use.

But then we were faced with the question, "Will it ever work?" When we decided to go into carbon, various doctors told us discouraging things.

> "It can't be made!"
> "One must have a floating disc; no fixed pivotal area."
> "You will never be able to put the leaflets inside the ring without breaking the ring." (This turned out to be our biggest challenge.)
> "Too expensive—carbon is like diamonds and it will be very expensive to manufacture a valve—the cost will be prohibitive." (It is true that when we introduced this valve, it was already twice as expensive as the most expensive valve on the market.)
> An expert in valve design said, "It won't work. You have no flow around the pivot guards."

When we did start collecting our animal data, we had our first good sign. We had valves working in animals for rather long periods of time, and we implanted valves in a total of 33 calves. Finally, our good friend Dr C. Walton Lillehei told us that we had done more animal work than anyone else, and we proceeded.

It is important to bear in mind that when we did our first human implantation we had certain guidelines from the Food and Drug Administration, but no regulations. The law had been enacted in May 1976, but the actual rules and requirements were not written until after we began our clinical studies.

These studies proceeded very well and rapidly with Dr Demetre Nicoloff doing the first implantation in Minneapolis on October 3, 1977. Our friends throughout the world helped us in evaluating this new and exciting valve, and the results were excellent. Although we asked them only to do a few valves, many of them insisted on continuing the study with more and more patients. At that time we had no restrictions from the FDA, but when the guidelines were finally put in place (July 1981), the requirements called for only 250 implantations. By that time we already had several thousand. This caused some undue concern at the FDA, and it looked like our young company with its great valve was going to be closed down. Fortunately, our friends helped us with the FDA,

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and we were able to overcome this difficulty in about 18 months.

On the other hand, the reception we got from certain physicians were very difficult. It almost looked like the saying "It will never work!" was about to come true. "We need 5 years of data," we heard from some. "We have asynchronous closing—this is bad," from others. And still others said: "This valve is too complex—we have three pieces instead of two pieces." For a while it appeared as if we had come to the end. The clinical results, however, were overwhelming, and today the St. Jude valve is the most prescribed valve; almost a quarter of a million implantations have been performed around the world over the last 12 years without a single design change.

The Design Simplicity and Clinical Elegance of the St. Jude Medical Heart Valve

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St. Jude Medical was founded in July 1976 to develop a new, central-flow, pyrolytic carbon, bileaflet prosthetic heart valve. Earlier concepts of a bileaflet valve that provided a design basis included the graphite-benzalkonium-heparin coated, central-hinging, silicone/Teflon bileaflet Gott–Daggett valve [1], which was first clinically implanted in 1963, and the titanium, low-profile, central flow, hingeless, double-leaflet Lillehei-Kalke valve [2], which was clinically implanted only once, in 1968. Pyrolytic carbon was selected as the material of choice for the St. Jude Medical valve components because of its excellent thromboresistance, wear resistance, and fatigue resistance.

The design objective of St. Jude Medical was to develop a valve that satisfied the features of an "ideal" valve. These features included minimal pressure gradient, hemolysis, turbulence, and stasis; limited regurgitation; and maximum thromboresistance and durability. In addition, the ideal valve had to be low in profile with a high effective orifice area to tissue annulus diameter ratio, and could not be dependent on chronic anticoagulation therapy.

The design of the St. Jude Medical valve evolved through concentrated development and testing efforts. Initial prototypes were constructed by September 1976 that consisted of both pyrolytic carbon orifice rings with the original "butterfly" pivot design concept and simple aluminum valves with two semicircular leaflets retained with pins. To optimize the pivot location of the leaflets, steady flow tests were conducted through October 1976 using the aluminum valve prototypes with the leaflets pinned in over 90 different configurations of pivot area separation and axial location.

The final design of a 26-mm bileaflet pyrolytic carbon valve was completed in November 1976. The key design features of this valve included an orifice ring with integral pivot guards that housed spherically radiused "butterfly" pivotal areas and two leaflets with integral retention "ears." The orifice pivot guards were positioned upstream of the orifice throat. The leaflets were allowed to rotate or pivot within the butterfly cavities via the ears. The unique pivot design permitted leaflet retention and control of leaflet opening and closing angles without the use of pins or struts, allowed for central opening, and permitted complete washing around all exposed leaflet surfaces.

Major manufacturing issues were resolved and a prototype of the 26-mm carbon valve was made by February 1977. Critical dimensions, tolerances, and clearances were refined for the 26-mm valve by May 1977 through intensive steady flow, pulse duplicator, and flow visualization studies. The design for the full range of valve sizes (19 mm through 31 mm) was final by September 1977.

In vitro performance studies of the St. Jude Medical valve demonstrated effective hemodynamics and durability. Pressure gradients were found to be lower than those of the Hancock, Björk-Shiley, Starr-Edwards, and Lillehei-Kaster valves, based on steady flow and pulse duplicator studies. In addition, a high flow orifice to tissue annulus diameter was shown. Flow visualization revealed central flow with minimal turbulence, stasis, and vortices [3]. Based on accelerated life testing, the valve life was projected to exceed 100 years with intrinsic strength to withstand over 20 times the maximum physiological pressures before fracture [4].

In vivo animal performance studies of the St. Jude Medical valve confirmed its readiness for human implantation. Calf studies were conducted at the University of Texas, University of Minnesota, and the Mayo Clinic. Valves were implanted in the tricuspid and mitral positions. No chronic anticoagulation therapy was administered. Calves were killed at 4, 8, 12, and 18 weeks. Results indicated no thromboembolism, no hemolysis, no mechanical failures, limited regurgitation, and no valvular interference with anatomical structures. Two tricuspid valves were found to have thrombosed, and two developed thrombus without impeding leaflet motion. Pressure gradients increased as the calves grew [5].

The final design features of the St. Jude Medical valve defined its simplicity and functionality. The bileaflet configuration provided central, evenly distributed flow patterns with small areas of flow separation, minimal flow resistance, low profile, large effective orifice area, and ease of surgical implantation. The highly polished, silicon-alloyed pyrolytic carbon material used for both the orifice and leaflets provided maximum thromboresistance, durability, and wear resistance. The controlled dimensional clearances between the orifice and leaflets provided complete washing of all exposed surfaces, minimal hemolysis, limited regurgitation, and free leaflet motion. The seamless, double-velour Dacron sewing cuff provided rapid and controlled tissue ingrowth and minimal thrombosis and thromboembolism. The optimally spaced and positioned pivot locations provided full, stable, responsive leaflet opening and closing and minimal leaflet exposure. The orifice butterfly and leaflet ear pivot geometries permitted "free floating" leaflet rotation and

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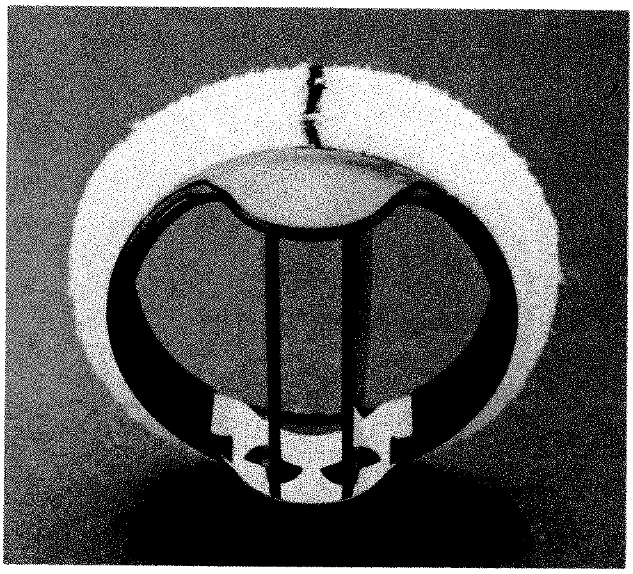

Fig 1. St. Jude Medical Bileaflet Prosthetic Heart Valve.

retention without the use of hinge pins or struts and full 85-degree opening and 30 to 35-degree closing.

The clinical elegance of the St. Jude Medical heart valve has continued to be proven since the first human implantation occurred in October 1977. Over 200,000 St. Jude Medical valves of the same design have been implanted. The low clinical complication rates are best illustrated by the results of a 10-year follow-up of 1,275 patients (94% followed) by Arom and associates [6], in which the rate for thrombosis was 0.05% per patient year; for thromboembolism, 1.0% per patient year; for hemorrhage, 0.78% per patient year; and for paravalvular leak, 0.12% per patient year.

The efficient hemodynamics of the valve are best illustrated by the cardiac catheterization data obtained at least 30 days postoperatively from primary and secondary clinical study centers and reported by Lillehei [7]. The aortic valve peak pressure gradients were reported as 11.0 ± 2.89 mm Hg for 19-mm valves to 2.07 ± 0.82 mm Hg for 25-mm valves. The mitral valve pressure gradients were 1.81 ± 0.57 mm Hg for 27-mm valves to 2.2 ± 1.28 mm Hg for 31-mm valves. The aortic valve effective orifice areas (Gorlin) were 1.38 ± 0.15 cm^2 for 19-mm valves to 2.62 ± 0.17 cm^2 for 25-mm valves. The mitral valve areas were 3.03 ± 0.37 cm^2 for 27-mm valves to 4.30 ± 1.15 cm^2 for 31-mm valves.

The long-term clinical durability of the valve is best illustrated by the absence of any reported pattern of structural failure caused by design or materials and the absence of any measurable wear or device deterioration on valves explanted at 8.5 years and at 11.0 years and analyzed by scanning electron microscopy.

In summary, the central-flow, pyrolytic carbon, bileaflet St. Jude Medical heart valve (Fig 1), which has its roots in the earlier bileaflet concepts of the 1960s, represents a simple yet highly functional valve design whose excellent clinical performance since 1977 attests to its clinical elegance. Although the valve satisfies many of the features of an ideal valve such as long-term durability, nonthrombogenicity, and hemodynamic efficiency, its clinical dependence on chronic anticoagulation persists. The clinical need remains for an ideal prosthetic heart valve that does not require chronic anticoagulation.

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Elimination of the Cloth Sewing Ring–Metal Interface in an Effort to Decrease Thromboembolism

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Development of caged-ball cardiac valve prostheses allowed total replacement of diseased valves [1, 2]. Clinical use of these prostheses resulted in substantial hemodynamic improvement in most patients with symptomatic acquired cardiac valvular disease [3, 4]. However, long-term experience with these caged-ball prostheses demonstrated a substantial incidence of thromboembolic complications, even with the use of anticoagulants. In a 5.5-year follow-up of a large group of patients receiving mitral valve replacement, deaths due to thromboembolism were not exceeded by any other cause of late death [5].

Therefore, attempts were made to design a mitral valve prosthesis that would not be associated with such a high incidence of thromboembolic complications. Because it is believed that most thrombus formation associated with valve prostheses originates at the junction between the cloth sewing ring and the metal of the prosthetic base [6], this cloth–metal interface was eliminated by covering the entire base and sewing ring of a caged-disc mitral valve prosthesis with Dacron velour, a loop-pile that encourages the ingrowth of fibrous tissue [7]. Originally, cage legs of the prosthesis were covered with Teflon [8]. Long-term experience with this prosthesis (the Beall-Surgitool mitral valve prosthesis) demonstrated a low incidence of thromboembolism, even without the use of anticoagulants [9]. This low incidence of thromboembolic complications with the prosthesis was confirmed in a number of centers [10–13], and efforts then were aimed toward improving the prosthesis.

First, the extruded Teflon disc (Model 102) was changed to a compression-molded disc (Model 103), due to reports of wear problems with the less dense extruded disc. Next, the primary and secondary orifices of the smaller sizes were enlarged (Model 104), due to reports of higher than desirable gradients across these sizes. Finally, efforts were made to construct the prostheses from more durable materials.

Pyrolite carbon was used for coating both the cage legs and disc, while the Dacron velour covering of the base and sewing ring remained unchanged (Model 105). Wear studies in calves with scanning electron microscopic analysis demonstrated less than 0.8% penetration of the Pyrolite carbon in 1 year. Repeat cardiac catheterization of patients with this prosthesis demonstrated insignificant gradients across these prostheses, which had incorporated the enlargement in primary and secondary orifices in all sizes, and again an exceedingly low incidence of thromboembolic complications was seen [14].

However, an unforeseen problem developed, in that as a material is made harder to reduce wear, ductility is decreased and the material becomes more brittle. If Pyrolite carbon is mishandled, for example, if it is dropped or the cage legs of the prosthesis are bent, it can be cracked, which then concentrates stresses on the wire of the cage leg underlying the crack. This phenomenon resulted in six instances of fatigue fracture of a cage leg with escape of the disc. This was corrected by increasing the diameter of the wire of the cage legs underlying the Pyrolite carbon, and a package was developed in which the prosthesis could be sterilized by either steam or ethylene oxide, thereby protecting the prosthesis until the time of implantation (Model 106).

Due to medicolegal concerns regarding all implants, the company originally manufacturing the prosthesis sold its entire line of heart valve prostheses to a smaller company. However, the valve prosthesis did not fit the product line of this company, and the valve prosthesis was sold to a still smaller company. Technically, the prosthesis is still on the market, but inventory of sizes has become so small that its use is no longer feasible.

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Implantation Techniques: A Primary Consideration in Valve Surgery

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Results of prosthetic valve operations vary substantially between surgical groups reporting on experiences with the same prosthetic valve. Conceivably, a "good" valve will perform poorly when implanted with shoddy technique or faulty judgment.

Site Preparation

Calcium removal is accomplished with a blunt curette, crushing nodules with a hemostat. This preserves the fibrous shell of the calcium nodules, thus providing a better suture retention site. Sharp dissection removes this fibrous base. Excessive debridement at the mitral annulus site, especially posteriorly, predisposes to atrioventricular rupture [1]. Excessively deep removal of the papillary muscles and excessive elevation of the heart out of the pericardial cavity, especially after valvular replacement, also predispose to ventricular rupture [2]. In the absence of excessive calcium and fibrotic obstruction, a case can be made for the retention of the posterior leaflet [2]. Occluder dysfunction will occur if improperly resected chordae or excessively long tails on suture knots find their way into the pathways of moving valve components [3].

Valve Sizing

There have been admonitions against oversizing prosthetic heart valves during valve replacement since the dawn of valve surgery. This is especially true with the newer central flow valves (single pivoting disc or bileaflet valves). Under usual physiological demands, with the exception of the smallest valves, there is no clinically significant increase in cardiac output or difference in pressure gradients between valves of adjacent sizes. There is no advantage in inserting a valve one or two sizes larger than necessary. A relaxed heart, after removal of pathological annular tissue, presents an annulus excessively larger than its normal physiological condition and is a tempting target for an oversized prosthesis. A surgeon must predict the heart's left ventricular contour after recovery to avoid oversizing [4]. Insertion of an oversized prosthesis stretches the annulus and can lead to rupture of the ventricle once the heart resumes function [5]. Chaux and Blanche [6] state that the use of an oversized prosthesis may result in applications of excessive force, which could cause dislodgement of the valve leaflets or cracking of the valve ring in the St. Jude Medical prosthesis.

Conventional wisdom dictates that whenever in doubt about tissue clearance, use a smaller prosthesis. In a narrow aortic root a Konno-type procedure is advisable [7]. The Lillehei-Kaster and Omniscience valves can be rotated after implantation for optimization of orientation, relative to the pathological anatomy of the heart. Orientation can compensate to some degree, in mechanical and tissue prostheses, for the effects of oversizing.

Cortina and associates [8] reported on serially decreasing thromboembolic rates with three different prostheses between 1980 and 1983. Although the paper fails to address the statistically significant differences in preoperative patient characteristics within these groups, one notes that during the short course of the study (3 to 4 years), the mean implant valve size decreased by more than 2 mm (one valve size). This could explain the differences in thrombotic complications among the three patient groups, as the smaller the mean valve size, the lower the complication rate [9]. Starek and co-workers [10] warn of the dangers of oversizing, particularly in patients with an enlarged myocardium. For single-disc valves in the mitral position, when the larger orifice is oriented posteriorly, a smaller valve is recommended to avoid possible tissue interference, particularly when myocardial shrinkage is anticipated. An anterior orientation minimizes the potential of disc/tissue interference with the shrinking, recovering myocardium. Only severe septal hypertrophy would conceivably cause interference in this orientation. The difference in clinical results was apparent from a review of 18 centers [11] in a largely North American patient population study, where the average mitral size ranged from 26.5 mm to 30.5 mm. Generally, the surgeons using larger valves with a posterior orientation reported higher thromboembolic complication rates.

Tilt Dysfunction

A large prosthesis can be wedged into a smaller orifice by tilting it out of the plane of the recipient orifice, distorting its presentation to the axis of blood flow. This may exceed the normal restraints of the prosthesis design. Antunes and colleagues [12] reported occluder dysfunction with a tilted prosthesis, causing the occluder to open beyond the axis of flow. "Over-opening" can occur with pivoting disc valves as well as with bileaflet valves. The St. Jude Medical valve has the largest opening angle of all valves, thus making it more susceptible to dysfunction with a tilted implantation. An oblique tilt of 5 or more degrees, which is difficult to visualize at operation, can result in one of the leaflets opening past the axis of flow with delayed (asynchronous) closure and resultant regurgitation.

Orientation

Valve orientation sometimes involves a trade-off between optimal hemodynamic performance and the risk of tissue

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interference. Ventricular hypertrophy, thickened mitral valve structures, hypertrophied septum, and small aortic root can affect flow patterns so that the hemodynamic ideal cannot be achieved. A compromise must be made.

Aortic Valve

When inserting an aortic pivoting-disc prosthesis, there seems to be agreement that the major orifice should be directed in a general anterior orientation. These recommendations vary over the 180-degree anterior spectrum [12–15]. Avoidance of tissue interference is the primary consideration.

Ross and Roberts [16] and Chaux and Blanche [6] believe that incomplete or phased opening of the St. Jude Medical prosthesis can be brought about by interference with a hypertrophied septum or the anterior leaflet of the mitral valve, and suggest placement of the valve with the leaflets perpendicular to the septum.

Mitral Valve

The orientation of five types of pivoting-disc prostheses was studied by Jones and associates [17]. Posterior orientation (major orifice toward the ventricular free wall) showed physiological velocity profiles and laminar flows. Björk [18] recommends this posterior orientation because of hemodynamics. Hall [15], however, recommends an anterior orientation (large orifice toward the septum) to eliminate the possibility of disc interference with hypertrophied structures on the mural side. Our studies [11] indicate the anterior orientation is more forgiving to patient-related anomalies and surgical factors, especially when oversized valves are used and when myocardial shrinkage occurs during the recovery stage.

Chaux and Blanche [6] recommend placing the leaflets of the St. Jude Medical valve perpendicular to the natural commissures to decrease the incidence of asynchronous leaflet closure.

Suturing Techniques

Too often the sewing ring of a prosthesis is treated as a gasket by which one may attach a hard housing ring to soft heart tissues. The sewing ring should be soft and compliant to absorb the forces of the heartbeat on the suture/tissue attachment. To take advantage of the sewing ring compliance, sutures should be placed no deeper than the outer third of the sewing ring. Suture "bites" placed more deeply, toward the housing ring, will result in the loss of most of the fabric compliance. This leads to more stress developing at the suture sites of the annular tissue, predisposing to compromised attachment and possible paravalvular leaks.

The selection of suture materials, the placement of stitches (continuous, interrupted, horizontal, or vertical mattress), and the use of pledgets is most subjective. Literature references applaud all conceivable combinations. The best lesson to learn is to use great care and be comfortable with the technique you use.

Summary

Clean site preparation for a prosthesis is mandatory to avoid tissue interference with the prosthesis. Oversizing of a prosthesis is fraught with peril. In all types of prostheses, orientation has importance. A prosthesis is designed with consideration for axial flow. Tilting the valve in implantation will likely result in a dysfunctional valve. The sewing ring serves not as a gasket but as an additional factor that increases the possibilities of success of a properly implanted valve by taking advantage of its naturally compliant features.

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Eighteen-Year Evolution From the Lillehei-Kaster Valve to the Omni Design

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The Lillehei-Kaster (LK) cardiac valve was implanted by C. W. Lillehei in 1970 [1], in an attempt to overcome the limitations of other valvular designs of the day. The LK valve consists of a free-floating, pivoting disc made of pyrolytic carbon, which is inserted into an integrally machined titanium housing. The disc moves to an opening angle of 80 degrees, and is retained by two curved projections which extend above the valve. The hingeless disc, which rotates freely within the housing, is one of the first attempts to achieve central flow. The overall profile was substantially reduced from earlier valve configurations to minimize the risk of anatomical interference. The disc configuration has been exceptionally durable, with only 1 case of disc fracture (which was successfully reoperated) reported in the literature [2] out of more than 50,000 implants worldwide. The integrally machined titanium housing (no welds or solders) has had no structural problems through its 18-year history.

The clinical results with this prosthesis are generally good. A recent study by Olesen and colleagues [3] involving 876 patient-years in patients who received mitral valve implants between 1972 and 1980 showed 10-year freedom from valve-related morbidity and mortality to be 66%, and from thromboembolism, 76%. However, the in vivo hemodynamic performance of the LK valve has been poorer than anticipated. Various authors [1] noted that high pressure gradients persist in smaller valves, especially in those patients with a narrow aortic root. Nitter-Hauge and co-workers [4] noted that the LK valve had a less favorable ratio of effective orifice area to tissue annulus diameter.

Continued engineering studies demonstrated a few areas that could be improved, and a second-generation prosthesis evolved as the "Omni" design. The ratio of nominal flow orifice (ie, disc diameter [D]) to tissue annulus diameter (TAD) was the most obvious improvement area. Studies using laser-Doppler anemometry and analysis of flow profiles demonstrated that three other critical dimensions must be optimized [5]: the opening angle, the curvature of the disc, and the eccentricity of the pivot axis. Increased opening angle results in more uniform, less turbulent flow, and hence lower pressure gradient. Paradoxically, the greater the opening angle, the higher the energy loss due to regurgitation. Although disc opening of approximately 60 degrees produces an optimum combination of pressure gradient and low regurgitation (eg, the Björk-Shiley convexo-concave valve), an 80-degree opening was maintained in the Omni design to allow for reserve opening during higher cardiac output. The potential increase in regurgitation is minimized by the low leakage rate permitted in this design.

Disc curvature permits alignment of the leading disc edge parallel to the flow to minimize turbulence. However, excessive curvature will result in turbulent flow. Optimization of the pivot-axis eccentricity, which dictates the velocity and turbulence profiles in the major and minor orifices, minimizes stasis zones and shear stresses.

The Omni design optimization encompassed increasing the ratio of D/TAD and replacing the retaining "prongs" by lower, rounded shields to minimize the valve's profile and the risk of impingement. A thinner (lower mass), convexo-concave disc with an optimized curvature of 0.05 D resulted in a lower pressure gradient and accelerated the opening/closing response. The pivot axis eccentricity was lowered to 0.17 D from 0.23 D, thus improving the flow in the minor orifice. These changes were incorporated in the design of the Omniscience valve (Fig 1).

In vitro studies by Stein and associates [6] showed that these changes result in a decrease of 26% in the systolic pressure gradient from the previous LK design. Scotten and colleagues [7] found that in terms of transvalvular energy loss, the Omniscience valve was superior in performance to the Medtronic Hall, Björk-Shiley convexo-concave, and St. Jude Medical prostheses. Recent in vitro work by Knott and associates [8] confirms the importance of overall energy losses and the serious implications of high leakage flow for cardiac valve prostheses. The Omni design has demonstrated superior results in this regard.

The Omniscience Premarket Approval studies, scrutinized by the Food and Drug Administration, show that actuarial survival at 5 years for patients at risk is 82% for patients undergoing aortic valve replacement and 73% for those undergoing mitral valve replacement, while the 5-year freedom from thrombotic complications (valve thrombosis, thromboembolism, and transient ischemic attacks) was 94% and 95% for patients undergoing aortic and mitral valve replacement, respectively. Comparatively, Damle and co-workers [9] report an overall 5-year thrombotic-free rate, including transient ischemic events, to be 87% for all patients (84% for aortic valve replacement) and 90% for mitral valve replacement).

In 1983 and 1984, two European studies [10, 11] reported extremely high thrombotic complication rates with certain mitral sizes. Their experiences were in sharp contrast to the Premarket Approval findings. These results became the focus of much attention [12–14]. It was revealing to note that these high complication rates were

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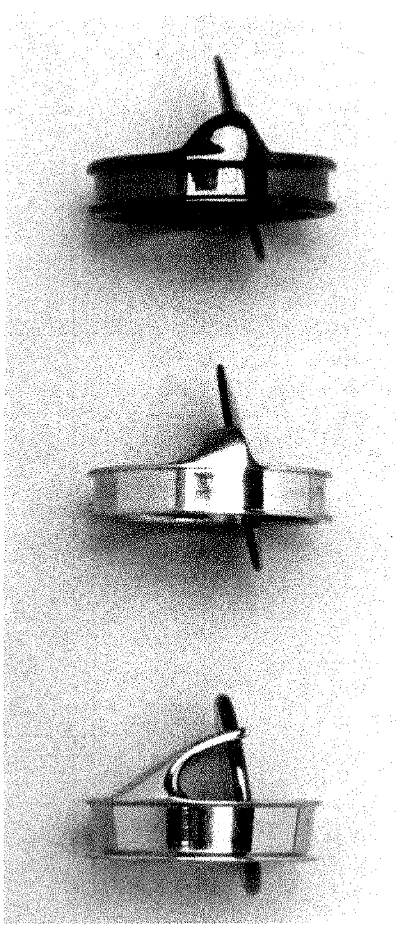


Fig 1. Eighteen-year evolution of the Omni design. This photograph shows in ascending order the changes that have occurred from the development of the Lillehei-Kaster to the Omniscience and finally the Omnicarbon valve designs.

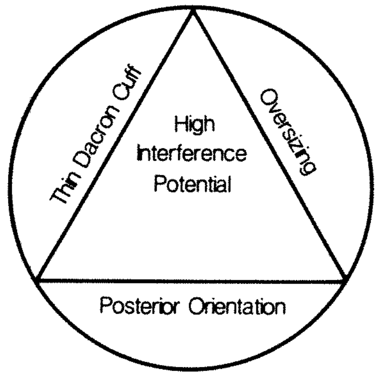


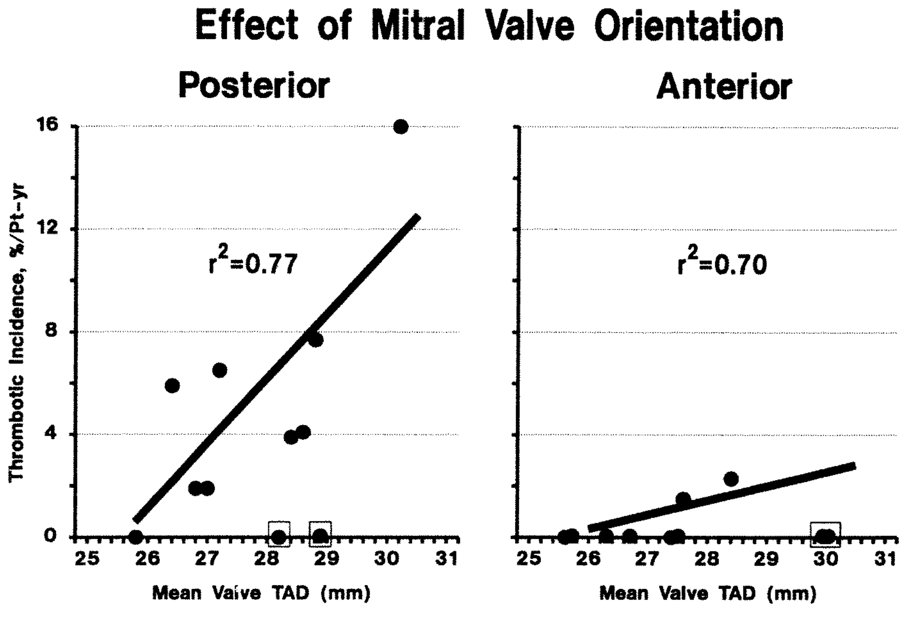
Fig 2. Factors in mitral valve thrombosis for the Omniscience valve before 1982. A combination of thin suture ring, a posterior orientation of the large orifice, and oversizing of the cardiac prosthesis greatly increase the risk of potential interference.

associated primarily with 29-mm and 31-mm mitral valves, but not with the 33-mm valve, which has the same housing/disc size as the 31-mm valve, but a 2-mm thicker sewing ring. This strongly implicated the clearance between the mechanism and tissue as a factor. Multicenter studies [15] revealed that posterior orientation of the major orifice results in a significantly greater incidence of valve thrombosis and thromboembolism (Z test, $p < 0.05$). It was thus concluded that the combination of orientation, the thinner Dacron sewing ring (used in the Omniscience valve before 1982), and oversizing substantially increases the incidence of thromboembolism (Fig 2).

Figure 3 shows reasonable correlation between size and thrombotic complications, with significantly higher thrombotic rates in the posterior orientation. The correlation is not very high because other factors presumably come into play, eg, preparation of the annulus, preservation of the mural leaflet/chordae, and suturing technique.

Consequently, to reduce potential interference, the Omni design was modified in November 1981 to incorporate greater clearance between the moving component and the ventricular tissue. The housings of the 29-mm and 31-mm valves were "down-sized" by 2 mm with a thicker

Fig 3. Correlation of size, orientation, and thrombotic complications. This graph shows the strong influence of oversizing in a posterior orientation on thrombotic complications. The partial correlation ($r^2 < 1.00$) likely demonstrates the influence of surgical technique/preparation factors in this relationship. (TAD = tissue annulus diameter.)



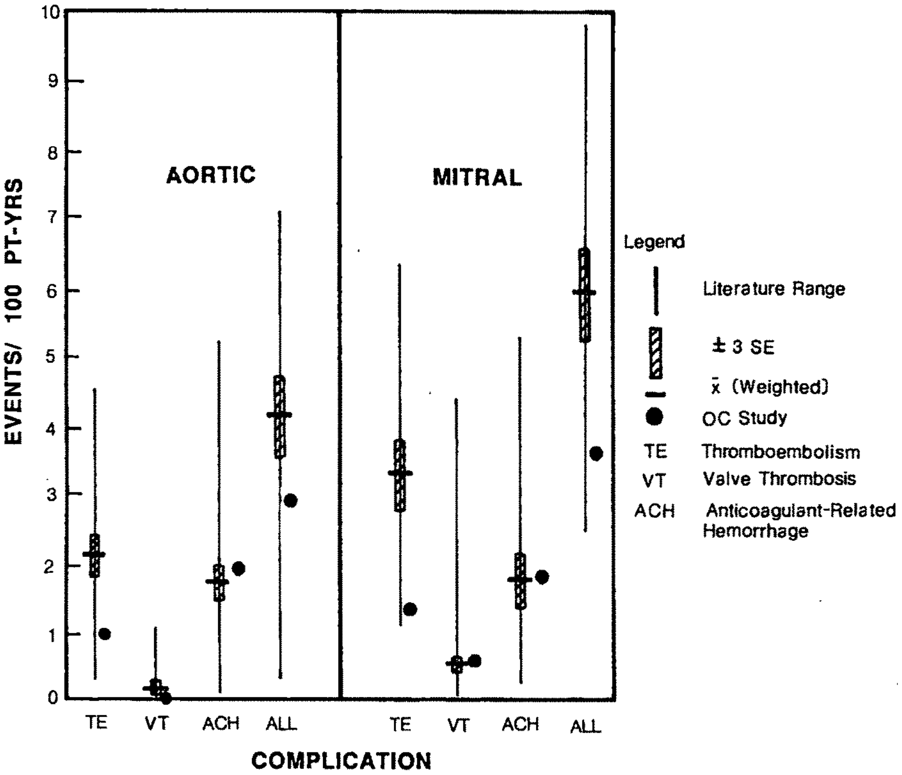


Fig 4. Comparison of Omnicarbon to 1987 literature survey by Edmunds [19], summarizing the incidence of thromboembolic and hemorrhagic complications as calculated from weighted summary data reported by Edmunds for mechanical cardiac valve prostheses. The low thromboembolic rate for the Omnicarbon valve is achieved without the risk of high anticoagulant-related hemorrhage. (PT-YRS = *patient-years;* SE = *standard error.)*

Teflon sewing ring to make up the difference. This serves as an additional "buffer" from myocardial interference, particularly in cases of potential oversizing after heart volume reduction during patient recovery. The combination of the earlier thin Dacron sewing ring, the continuous suture technique, and degenerative tissue resulted in a higher incidence of perivalvular leak in a few European centers [10, 11]. The higher compliance of the thicker Teflon sewing ring also alleviated this unusually high perivalvular leak rate [16].

Historically, fixed-hinge valve designs (metal/polymer interface) were prone to a high incidence of thrombotic complications [17]. The original Lillehei-Kalke fixed-hinge bileaflet valve design was reported in 1967 [18]. Its manufacture was abandoned until a less thrombogenic material could be found. The advent of Pyrolite, which demonstrated an excellent record of biocompatibility, rendered this design a viable one (St. Jude Medical valve, 1977). Essentially, Pyrolite turned the unsuccessful fixed-hinge design into a successful one. It stands to reason that one should advance this conclusion one step further by using Pyrolite in a design with no fixed hinges, and with a proven clinical record in a metal configuration. Therefore, the time-tested, fine-tuned Omniscience design features were incorporated into an all-carbon structure, the Omnicarbon valve.

Since 1984, over 7,000 Omnicarbon valves have been implanted. Clinical studies at five European centers, involving 354 patients, demonstrate an overall thromboembolic rate (valve thrombosis, thromboembolism, and transient ischemic attacks) of 1.3%/patient-year, of which 0.7% were transient events. No patient has been reoperated on for unacceptable hemodynamics or structural failure. Hematological results demonstrate the absence of any clinically significant hemolysis. Figure 4 shows how these results compare with those of a 1987 survey of the mechanical valve literature published by Edmunds [19] on the incidence of thromboembolic and anticoagulant-related complications.

To sum up, although no valve substitute is perfect, physicians and engineers perpetually strive for improvement. Without the 18 years of hand-in-hand cooperation, development of the Omnicarbon valve would have been impossible.

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Iatrogenic Factors in Cardiac Valve Evaluation

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Evaluations of cardiac valve prostheses on the basis of their hemodynamics, thrombogenicity, and durability generally attribute valve performance to the intrinsic characteristics of the device itself. Personal observations, anecdotal experiences, and occasional published reports relating to iatrogenic complications cause me to believe that these occurrences play a far more significant role in valve performance than is recognized in the literature.

Multiple factors influencing cardiac surgical outcomes, low complication rates, and the tendency for iatrogenic episodes to be unrecognized or undocumented all serve to obscure statistical correlation between the following technical abberations and their presumed associated complications. Nevertheless, the persistent incidence of thromboembolism, mechanical dysfunction, and structural failure—albeit low—mandates exercising every reasonable technical precaution to obviate the occurrence of these complications. Awareness of the potential hazards should reduce morbidity.

Hemodynamic performance of a mechanical prosthesis can be impaired by (1) inadequate tolerance between the poppet and the adjacent chamber wall (Fig 1), (2) interference with poppet excursion by adjacent chamber wall or remnants of the incompletely excised valve (commissures of the aortic valve and chordal tissue of the mitral valve (Fig 2), or (3) the shelf of remaining valve leaflet when mattress sutures are used. This type of impairment is difficult to diagnose, but diagnosis is facilitated by a radiopaque element in the poppet.

Interlocking of suture loops on opposite sides of the ring can result in a suture strand traversing the orifice beneath the poppet, which is easily obscured from surgical view (Fig 3).

Elongated suture ends, particularly when the knots are close to the orifice, can unravel and reach into the orifice so as to prevent complete closure. In valves that seat intraluminally (Cutter-Smeloff, Björk-Shiley, Medtronic Hall, St. Jude), episodes have been documented in which sutures have jammed the poppet and locked it in the closed position. Suture ends have also been documented to produce hemolysis after fraying into tassels. All of the aforementioned hazards of elongated knots and suture ends can be prevented by using a small soldering iron to transect the third knot and fuse the polyester suture into a smooth glazed bead to preclude untying.

Paravalvular leakage or disruption of the implanted prosthesis is commonly caused by infection, although iatrogenic factors may also contribute to its occurrence.

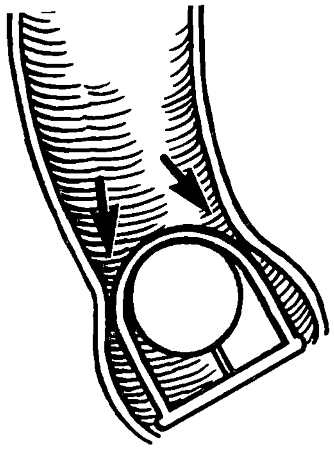

Fig 1. Obstructing caged ball poppet occupying a major portion of the aortic lumen.

Unequal tension can cause tissue tear when sutures (1) are tied with excessive tension, (2) are placed with tangential angulation, or (3) are placed at unequal tissue depth (Fig 4). Excessive (and potentially disruptive) tension can be placed on the suture line by attempting to adapt an outsized annulus to a smaller prosthesis. This complication can be avoided by augmenting the sewing ring diameter with a felt strip.

Thrombogenesis is reasonably initiated by foreign substances (such as tissue fat or glove powder), which may be deposited on the valve during implantation. The crevice between the cloth sewing ring and the tissue (which is promoted by mattress sutures) is a potential origin of clot propagation. Exposed knots and suture ends are also likely to be thrombogenic.

Mattress sutures are popular for valve implantation but

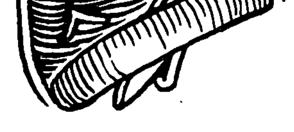

Fig 2. Tilting disc poppet restricted from full opening by a commissural remnant of aortic valve tissue.

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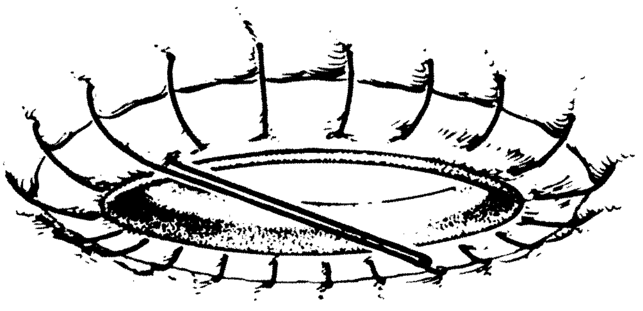

Fig 3. Postimplantation ventricular view (surgically obscured) of a suture that had passed through the loop of an opposite suture.

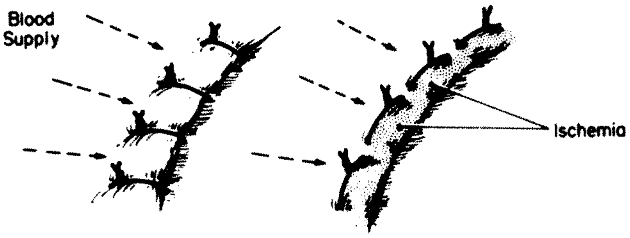

Fig 5. Mattress suture preventing perfusion of tissue at cloth interface as contrasted with the effect of radial sutures.

they embody three important detriments and potential hazards which are obviated by radial sutures. (1) They may impair optimal perfusion of the tissue–cloth interface, thus potentiating necrosis and paravalvular leakage (Fig 5). (2) Tissue remnants underlying the sewing ring can extend—or may even be extruded—into the orifice by the sandwiching action of a mattress suture, whereas this tissue is gathered peripherally into the loop of a radial suture. (3) The circumferential alignment of mattress sutures causes the peripheral edge of the cloth ring to roll upward, thus creating a potentially thrombogenic crevice between endocardial surface and cloth, whereas radial sutures flatten the edge of the cloth ring against the tissue surface (Fig 6).

Durability of the prosthesis can be impaired by intraoperative handling and manipulation during the seating process. Late strut failures are conceivably the product of iatrogenic stress. Poppet erosion and escape has resulted from erosion of the Silastic ball by (1) an abrasion on a caged-strut and (2) a suture accidentally looped around a strut.

The foregoing iatrogenic factors are worthy of recognition and reasonable preventive measures. Their proven occurrence must be taken into account in the process of evaluating prosthetic valve performance and could explain discrepancies in reported incidence of thromboembolism, paravalvular leak, and structural failure.

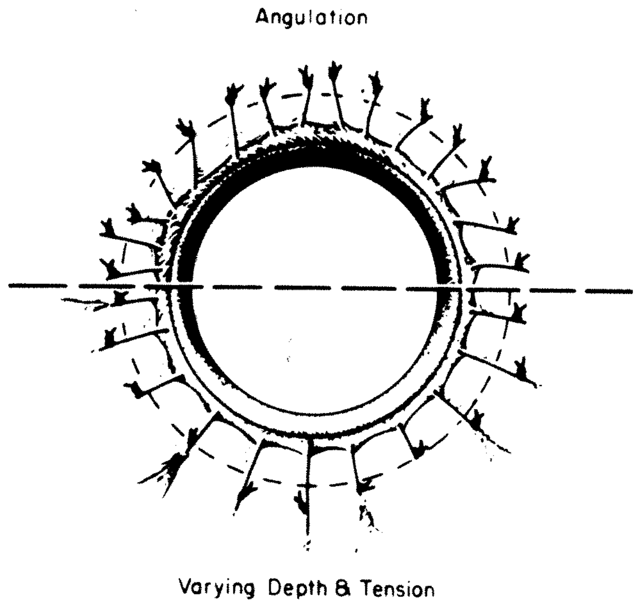

Fig 4. Angulated sutures (top) and unequal suture depth (bottom), showing how concentrated stress can promote avulsion.

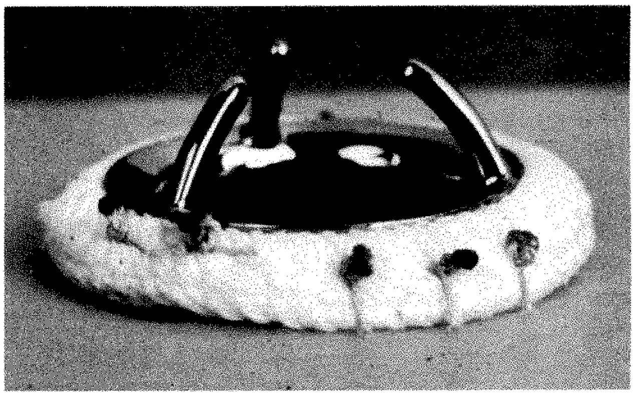

Fig 6. Valve implantation mock-up demonstrating the cloth suture ring rolled up by mattress sutures and flattening effect of radial sutures. Also demonstrated is the suture knot remnant after severing and fusing with a soldering iron.

Biopsy Assessment of Myocardial Protection for Valve Replacement Over the Last 24 Years

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In the study of myocardial protection for valve replacement over the last 24 years at St. Thomas' Hospital, we have evaluated protection by intraoperative myocardial biopsies and by postoperative clinical outcomes in terms of the incidence of low cardiac output and hospital mortality. Biopsy assessment has been by quantitative birefringence measurements of the ability of muscle fibers to respond to adenosine triphosphate and calcium on biopsy specimens frozen in hexane at −70°C, with measurements made on freshly cut cryostat sections studied under a polarizing microscope [1, 2]. The physiological significance of this test was checked by performing endomyocardial biopsies at the time of left ventricular (LV) angiography and comparing birefringence measurements of two groups of patients divided by means of eight physiological variables into normal and abnormal hearts. Separation of these by biopsy correlated with a probability of 0.001.

Biopsies were performed on 276 patients undergoing single aortic valve replacement. Of these, 214 showed no deterioration on biopsy assessment, 210 of whom had an uncomplicated recovery, with 4 having a low cardiac output. Of the 62 whose condition deteriorated, 51 had a low cardiac output, with 11 having an uncomplicated recovery. Biopsy correctly predicted low cardiac output in 95%.

Analyzing these results in detail (Fig 1), of the 19 patients who underwent biopsy who had intermittent perfusion between 1965 and 1968 with blood at 15°C, 63% had no deterioration on biopsy, and all made an uncomplicated recovery. Thirty-seven percent showed deterioration, and all but 1 of these had a low cardiac output.

Intermittent warmer perfusion at 30°C in 1968 and 1969 made the results worse, as 58% showed deterioration and 50% had a low cardiac output. Because of this, we changed to continuous perfusion with blood at 30°C. This improved myocardial protection, as 68% showed no deterioration on biopsy assessment during cardiopulmonary bypass. All but 2 of those that showed no deterioration had an uncomplicated course, but 32% deteriorated, with 26% having a low cardiac output. Changing to 32°C with a beating heart improved myocardial protection to 74% in the 61 patients who underwent biopsy.

When cardioplegic arrest was introduced in 1975 [3, 4], only a single infusion was given. Of 53 patients who underwent biopsy, 81% showed no deterioration, all of whom had an uncomplicated recovery, whereas 19% did show deterioration, with 13% having a low cardiac output. Multidose cardioplegia greatly enhanced myocardial protection, with 93% of hearts submitted to biopsy showing a satisfactory outcome both in terms of biopsy assessment and clinical outcome; however, all but one of the 7% of patients who showed deterioration had a low cardiac output.

One would expect the beneficial aspects of different methods of myocardial protection to be most apparent during double-valve replacements, with their longer ischemic times. This in fact has been the case. In small numbers submitted to biopsy in the groups protected by continuous coronary perfusion [5] and with single dose cardioplegia [6], there was deterioration of 29% and 33%, respectively. However, protection was improved by multidose cardioplegia, which reduced the incidence of deterioration to 11%. Analyzing overall clinical results of the double-valve replacements, the initial mortality in the 1960s with intermittent 15°C infusion was high (61%), but was improved by 30°C intermittent infusion (11%). Continuous 30°C perfusion was worse than intermittent infusion (50% mortality), although this improved once the temperature was raised to 32°C with the heart beating (15%). With single-dose cardioplegia, the mortality was unchanged but the incidence of postoperative low cardiac output increased to 16% as compared with 2% in the previous group. With multidose cardioplegia, both the mortality and the incidence of low cardiac output were halved (8% and 8%, respectively).

We have compared the results of patients undergoing aortic and mitral valve replacement alone with those in whom tricuspid valve operation was also necessary. With multidose cardioplegia for aortic and mitral valve replacements alone, 4/65 (6%) patients died due to low cardiac output. Twenty patients underwent an additional tricuspid valve repair, of whom 3 (15%) died of low cardiac output. The aortic occlusion times were significantly longer in this group, 143 minutes as compared with 124 minutes. In a separate study of 13 patients undergoing tricuspid valve repair with multidose cardioplegia, biopsy assessment revealed a 23% incidence of myocardial deterioration during bypass. These clinical and biopsy results indicate that even multidose cardioplegia did not adequately protect the myocardium during prolonged ischemia.

In summary, biopsy assessment of myocardial protec-

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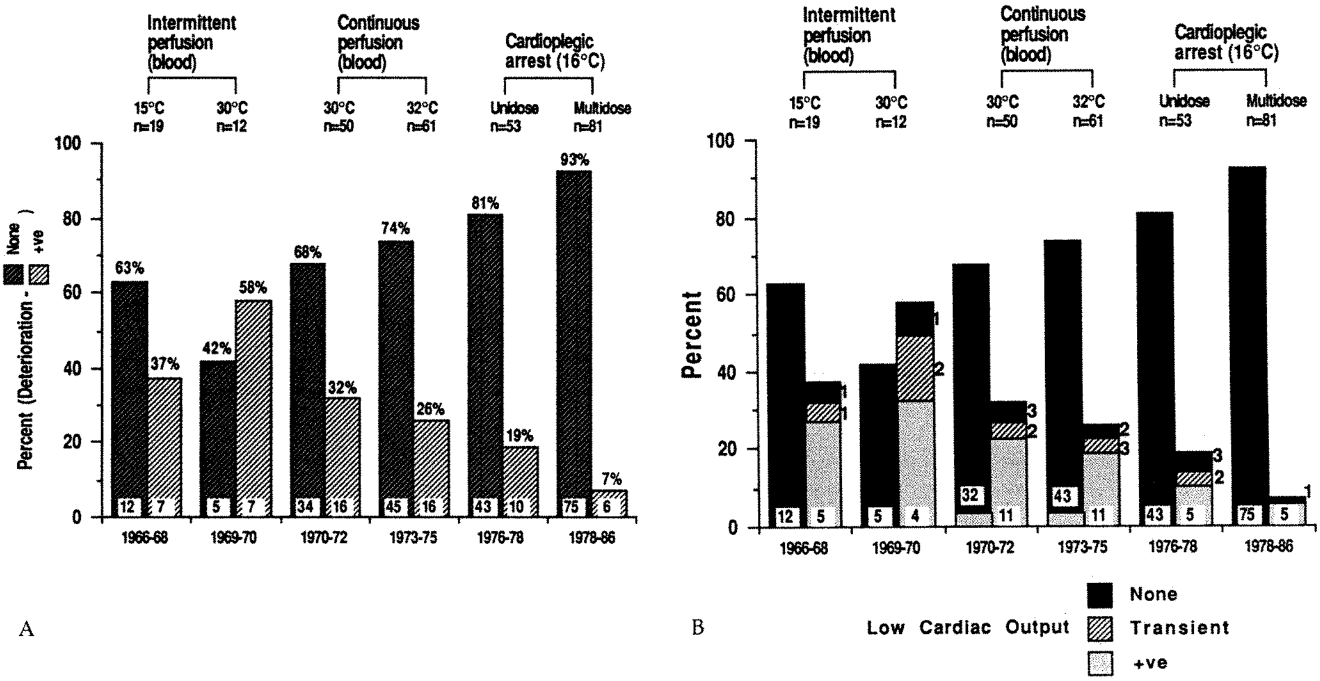

Fig 1. Assessment of the efficacy of different methods of myocardial protection. (A) Quantitative birefringence assessment of preservation made on left ventricular biopsy specimens obtained at the beginning and end of cardiopulmonary bypass from 276 patients undergoing aortic valve replacement between 1966 and 1986. (B) Postoperative clinical outcome of the same patients.

tion with quantitative birefringence measurements has proved a useful guide to the surgeon in evaluating his or her techniques over 24 years.

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The Versatile Homograft and Autograft Valve

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In this report I am using the old accepted term *homograft* rather than the more fashionable *allograft,* and I would suggest that the following be made clear about valve terminology. True biological valves have no man-made additions or distortions. So-called biological valves are hybrid creations of plastic, steel, and tanned leather and are appropriately called bioprostheses. They combine the virtues and disadvantages of biological and prosthetic valves.

My colleagues and I inserted our first homograft aortic valve freehand in June 1962 [1], within a year of the first mechanical Starr valve, which shares with it the distinction of over 20 years of follow-up. It is appropriate to remind ourselves that all valves (mechanical, biological, and bioprosthetic) are splendid for the first 7 years, so that a realistic appraisal of a valve's performance only becomes relevant after 10 years.

The advantages and disadvantages of the homograft are well known. Among the former is the total absence of emboli and the need for anticoagulant therapy with its attendant dangers. Other advantages have come to light, such as the virtual absence of sudden deaths, and the average lifespan of homografts before removal is certainly longer in our hands than that of their bioprosthetic counterparts. Other advantages include the low incidence of endocarditis, their successful application to young children, and their versatility in being applicable at all valve sites.

Quality of life is difficult to define and does not easily fall within the criteria that can be subjected to the newly introduced guidelines for the presentation of valve data. Nevertheless, all my aortic homograft patients, with one exception, when faced with a second operation, have asked for another homograft.

Without presenting a series of complex actuarial analyses relating to valve function, I would say that patient survival (which is what our patients are interested in and what should also be our primary concern) is better in our hands with a homograft than a mechanical valve (Fig 1). That to me represents the bottom line.

The only disadvantage of the homograft relates to learning the insertion technique. The problems of collection and processing have now been taken care of.

Tissue degeneration is the homograft's Achilles heel (Fig 2). Homografts cannot be faulted in design or functional performance, but it is to the problem of late degeneration that we need to direct our attention and that of the coming generation of biologically oriented surgeons.

We should not be carried away by the current uncritical wave of enthusiasm for viable valves. The transfer of living human tissue between donor and recipient represents a form of transplantation and obeys the rules of antigenicity and its inevitable immunological sequelae. The presence of living cells simply guarantees tissue integrity but does not ensure that the cells will persist. Only by retaining cellular viability can we ensure really long-term function of the homograft. We may eventually be able to seed the homograft with the patients' own cells.

In 1966 we inserted the first freehand valved homograft [2] for right ventricular outflow tract reconstruction 4 years after the first aortic homograft. This operation has in many ways revolutionized the treatment of complex cyanotic congenital heart disease, and no one questions the superiority of the homograft as a valved conduit, particularly in children, in whom it has given an impressive long-term performance and is clearly superior to the xenograft.

The homograft is also excellent in the low pressure tricuspid area, but it has given variable service in the mitral area, no doubt because of the need for some form of mounting material, which immediately turns it into a bioprosthetic device.

However, as a fully functional aortic root replacement without external restrictions, the homograft is finding increasing applications [3]. We first used this principle in 1972 in disruptive aortic root endocarditis, and have since used it in over 135 cases. The homograft root is easy to insert and is invariably competent. Early results suggest it may have a longer functional life than the conventional homograft.

Reserving the best for last, we offer autotransplantation of the pulmonary valve to the aortic position as a definitive form of aortic valve replacement [4]. Somewhat tentatively, we used this technique in 1967, having at that stage experienced our first homograft degenerative failures. It was clear that a permanent valve replacement has to be living, nonantigenic and of perfect design, and untreated by any damaging physical or chemical agents. Only the patient's own pulmonary valve fulfills these criteria.

Based on our experience with this valve, used in 294 patients operated on over 20 years, we believe the valve represents a permanent replacement, does not undergo degeneration or calcification, persists as a fully viable structure, and very likely has growth potential. Comparing it with our own series of homograft valves emphasizes its superior qualities. It can be used in any age group and as a mitral replacement in children; however, we believe its primary application is in the younger or very young age group, who with the present generation of valves, may face a recurring threat of embolism, to hemorrhage and sudden death, or repeated operations at 10- to 12-year intervals.

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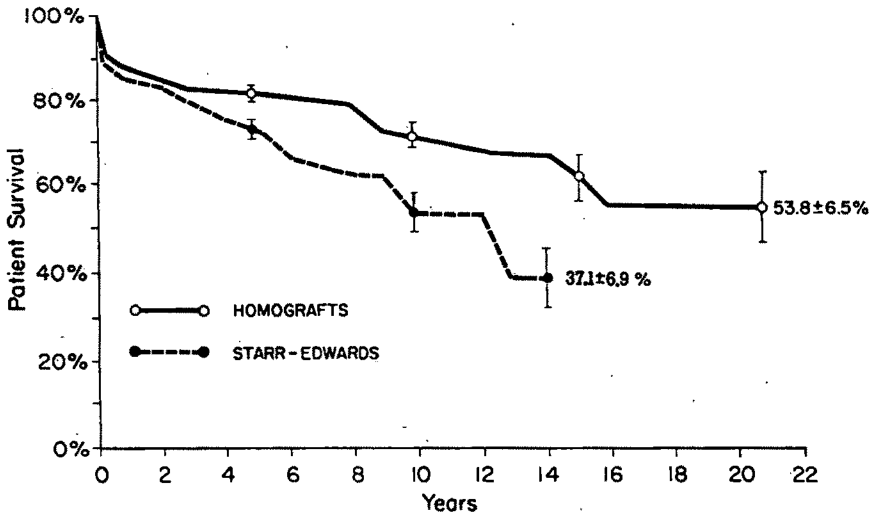

Fig 1. Comparison of actuarial survival with homograft and mechanical (Starr-Edwards) valves.

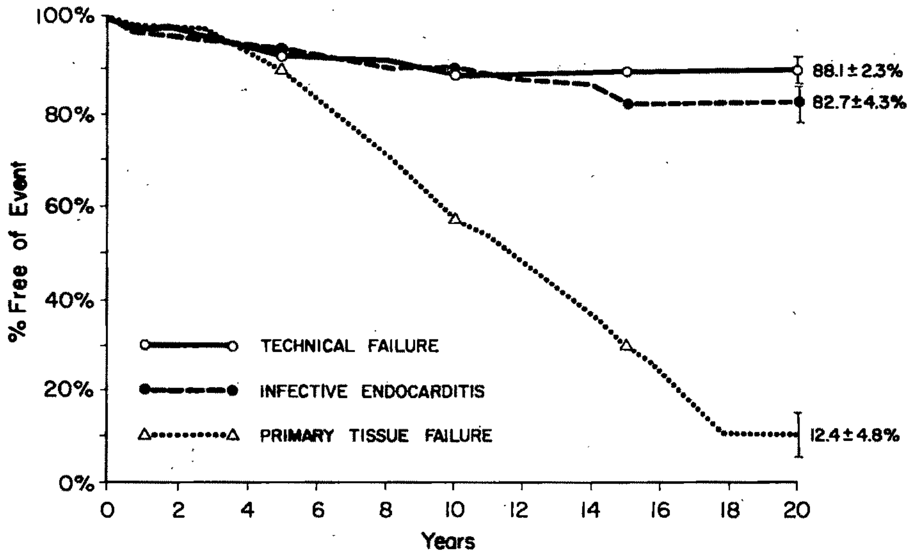

Fig 2. Freedom from technical failure, infective endocarditis, and primary tissue failure for homograft valves over 20 years of follow-up.

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Pioneering in Heterografts

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The idea of using animal valves came to our minds more than 25 years ago. We were unhappy with the available mechanical valves in many instances, even though I had inserted in Brussels, in mitral position in "francophone" Europe, the first Starr valve, given to us by my friend Albert Starr.

We were unable to build a satisfactory fresh homograft bank, not because of French law, but because of the adverse Parisian habit of postmortem examination. In the meantime, a better organization was set up in London, Aukland, and Bordeaux.

In 1963 we were still in the old Marie Lannelongue Hospital. At this time Carlos Gomez Duran, first in Oxford and later in Paris in Mathey's group, let us know of the good results obtained in England with dry-frozen pig aortic valves inserted into the descending aorta of dogs and of the unsuccessful attempt made by Gunning in 1964.

For 2 years, with Jean Langlois as assistant and Alain Carpentier as resident, we attempted to solve three problems linked with the insertion of the heterograft in aortic position. The first problem was to find available animals whose valve size would fit the human aortic valve. We selected porcine valves for average diameter, calves' valves for large size, and those of lambs for small size, especially for children.

The second problem was to prepare the valve. The anatomy of these animal valves differs from that of the human valve. One third of the aortic ring is formed by cartilage and the base of the right coronary sinus is muscular; all of this tissue must be excised. The third problem was to destroy the potential antigenicity of the valve while preserving its flexibility: a mercurial solution called Cyalite was first used. After three days in this solution the heterograft was washed out, divided, and stored in a saline solution.

Once these problems were solved, a 47-year-old patient with calcified aortic stenosis underwent operation: a porcine valve 25 mm in diameter was inserted without difficulty. The postoperative course was uneventful; the patient was discharged from the hospital without any diastolic murmur. This attempt was followed by 80 other aortic replacements through July 1967. But having crossed new frontiers, we also ran into new barriers.

Insertion of the valve was the first problem. The coronary cannulas that were still used at this time to perfuse the myocardium were making the insertion difficult. We followed the one-plane technique of Sir Brian Barratt-Boyes, who we promptly visited in New Zealand. Further, we modified the technique by using mattressed sutures in two planes; finally, the valve was set on a stent. In collaboration with Claude Planché we performed the first setting of these heterografts on a metallic stent surrounded by a Teflon ring.

Improving antigenicity was the second problem. We quickly exchanged Cyalite for Mercaptomeryl, a different and less aggressive mercurial derivative. Later in 1967 we started using formaldehyde. In fact, this has been a long period of multiple and various attempts.

During this period several major discoveries were made. There was no rejection of the graft; anticoagulation was not required, as it is for homografts; and tissue deterioration proceeded slowly, in contrast to the dysfunction of mechanical valves of that time. The place of heterografts became quite important because the setting on a stent allowed insertion in the mitral and tricuspid positions, as well as in a Dacron conduit, which then advantageously replaced the fresh human valved conduit that was impossible to obtain at this time. Our heterograft valved conduit was amazingly similar to what would later be called the Hancock conduit. We used it for the treatment of numerous congenital malformations (bad forms of tetralogy of Fallot, truncus arteriosus).

In addition to these new possibilities, we made some amusing and even predictive observations. In our voracious animal research as applied to humans we observed that boars did not have the same anatomical configuration as pigs and that, by contrast, the gorilla had an aortic valve anatomically and histologically similar to the human one—the histocompatibility is very close between the two species. (Autopsy of this gorilla was done at the zoo of Prince Rainier in Monaco.)

This period of the so-called heterografts ended when Sophie and Alain Carpentier suggested that glutaraldehyde was the best way to preserve and store these grafts. On this day heterografts became bioprotheses; they were

Table 1. Early Contribution to Heterograft (Hopital Marie-Lannelongue)

Contribution	Date of Operation	Manufacturer of Heterograft	Position
First heterograft (pig)	09/02/65	Homemade	Aortic
First heterograft (lamb)	07/06/67	Homemade	Pulmonary
First stent valve (pig)	03/09/68	Homemade	Aortic
First conduit + heterograft (pig)	04/28/70	Homemade	RV–Pulmonary artery

RV = right ventricle.

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no longer home-made but manufactured. We had worked only as trial and laboratory men. I did not have the chance to establish a French connection with our national industry; Alain Carpentier has been more lucky in the United States.

Our findings are summarized in Table 1. This shows our team's contribution to the birth and the development of heterografts.

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From Valvular Xenograft to Valvular Bioprosthesis: 1965–1970

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The research that led from the xenograft valve to the concept of the bioprosthesis is an example of the growing dependence of surgery on certain basic sciences. This presents the surgeon with two alternatives: either to learn the language of these sciences or to be relegated to the position of a manual worker.

The first successful xenograft valve implantation in humans was carried out in September 1965 by Jean-Paul Binet, Jean Langlois, and myself. Being responsible for the valve preparation [1], I chose a mercurial solution with which I had experimented 2 years earlier with Robert Judet, the inventor of the artificial hip; we used this solution to preserve homologous skin for reconstruction of joints and noticed very little inflammatory reaction, although skin was known to be extremely antigenic. Contrary to experimental findings and despite early good clinical results, the xenograft valves preserved in this mercurial solution tended to deteriorate after 6 months.

This early experience showed that the most important factor affecting valve durability was the method of preparation, and that the dream of graft regeneration by creeping substitution of host fibroblasts failed to materialize. The cellular ingrowth that did occur proved harmful, as the cells invading the graft tissue were most often inflammatory in nature. It became obvious that to prolong the durability of these valves it would be necessary to prevent cellular penetration. This aim was the subject of my research during the years 1966 and 1967, a research oriented in two directions: chemical treatment and mechanical protection.

Chemical Treatment: The Way to Glutaraldehyde Preservation

Because the inflammatory reaction observed in explanted xenografts involved mainly immunologically competent cells leading to collagen denaturation, I tried to find a chemical treatment capable of decreasing the antigenicity of the tissue and increasing its physicochemical stability. However, this was far beyond my capability in and knowledge of chemistry, and I found it necessary to go back to the university to obtain a PhD in biochemistry. I was 33 years old, 10 years older than the other students from whom I hid my true position as assistant professor of surgery so as not to compromise the reputation of cardiac surgery by the rather poor grades I got on the various examinations!

I worked on cross-linking inducing factors either to introduce cross-linkages into the tissue (acrolein, succinyldehyde, glyoxal, glutaraldehyde, formaldehyde, dialdehyde starch) or to reinforce cross-linkages (sodium borohydride). Among the many substances tested, glutaraldehyde, a product widely used in electron microscopy, appeared to be the most effective for decreasing the antigenicity and increasing the stability of the tissue as shown by subcutaneous implantation of treated tissue in the rat and by numerous physical or immunological tests. Based on these experiments, often forgotten today, glutaraldehyde was adopted as the method of choice in heterologous tissue preservation. My colleagues and I published our findings in 1969 [2].

Mechanical Protection: The Concept of *Greffe Protégée*

Because experimental and clinical data showed that inflammatory cellular penetration occurred chiefly at the graft-host interface, a physical barrier, ie, a thin cloth or a stent, was interposed between the host and the valve, and the aortic sleeve was covered with the same material (Fig 1). This concept of the *greffe protégée* and its combination with the first frame-mounted valve were introduced in 1966 and 1967, respectively [3, 4]. Various techniques were proposed over the years to solve the peculiar problems raised by the attachment of the muscular septum to the right coronary cusp in animals (Fig 2).

As a result of glutaraldehyde treatment and mechanical protection against cellular penetration, the valve is no longer a graft in the strict sense but a prosthesis. I coined the term *bioprosthesis* to recall its biological origin and its prosthetic fate [5]. The bioprosthesis falls somewhere between a graft and a synthetic prosthesis, and it is hoped that it incorporates the advantages of both. In contrast to the graft, the durability of the bioprosthetic valve becomes dependent on the stability and the inertness of the biological material and not on regeneration by host cells.

With Charles Dubost, my colleagues and I implanted the first bioprosthesis in March 1968 (Fig 3) [2]. The patient survived for 18 years with his original valve. Aware of the development of bioprosthetic valves, Albert Starr advised Edwards Laboratories to enter the field of tissue valves, and because of his recommendation, I was invited to Santa Ana in 1969 to present my work. I accepted the proposal of Will Perie, President of Edwards Laboratories, that I advise them in the development of a valvular bioprosthesis on the condition that the valve not

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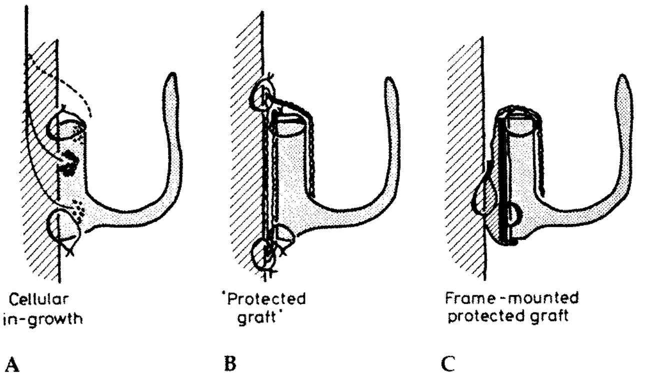

Fig 1. The concept of greffe protégée: *(A) penetration of host cells into graft (1965); (B) greffe protégée (1966); and (C) greffe protégée mounted on a stent (1967).*

be released on the market for a minimum of 4 years after implantation.

Warren Hancock was vice-president of Edwards Laboratories at the time, and he was present at this meeting. Some months later, he left Edwards Laboratories, thus freeing himself from my requirements. Without any restrictions, he developed the Hancock valve, which became commercially available in 1970. Hancock Laboratories made a tremendous contribution as far as mass production and popularization of valvular bioprostheses were concerned, a little too much popularization in my opinion, as very few people at that time listened to my words of caution in regard to the long-term fate of these valves, particularly in children.

This previously unpublished story is interesting mainly because it points out the foresight of Albert Starr, who must be credited, among his other contributions, for having introduced valvular bioprostheses to the United States without regard to the effect on his own valve. Much of the remainder of the story, ie, the development of bioprosthetic valves, whether porcine valves or bovine pericardium, whether high profile or low profile, whether yellow or blue, is known, but not its ending. Twenty years later, we know that the aim has been only partially achieved. Although low thrombogenicity has been confirmed, an acceptable stability has been observed only in patients older than 35 years. We know that the older the patient, the longer the valve durability. Calcification of the tissue remains a stumbling block in younger patients. The current efforts of my wife, Sophie, who has helped me since 1974, and myself are directed toward the development of chemical methods of calcium mitigation so that, one day, children will have the benefit of a durable, nonthrombogenic valvular prosthesis.

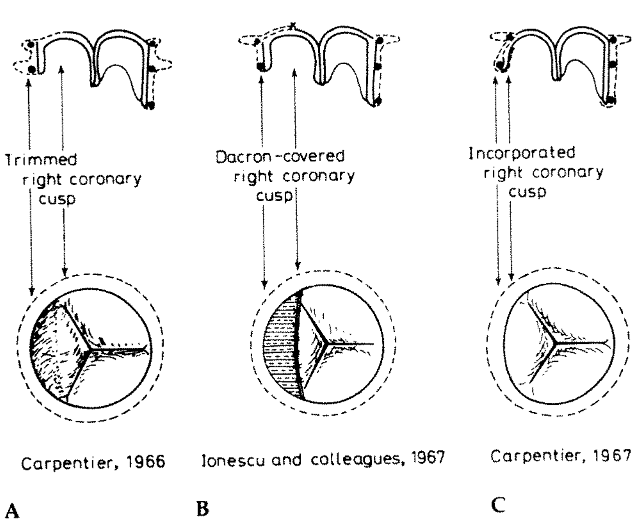
Trimmed right coronary cusp
Dacron-covered right coronary cusp
Incorporated right coronary cusp
Carpentier, 1966
Ionescu and colleagues, 1967
Carpentier, 1967
A
B
C

Fig 2. Stents were introduced in 1966 before glutaraldehyde preservation. Several techniques were used to reinforce the right coronary cusp (B, C), which was made fragile by trimming (A).

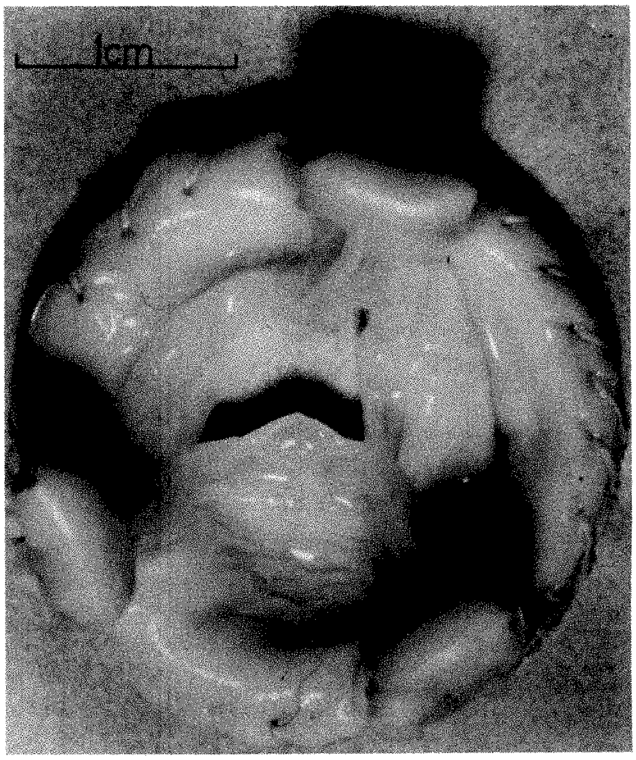

Fig 3. First glutaraldehyde-preserved, frame-mounted porcine valve implanted in a human. Note that the aortic sheath and the struts were not covered with fabric in this early model.

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Heterologous Heart Valves: Past, Present, and Future

Sheldon O. Burman, MD

The purpose of this paper is to document the events culminating in the first successful human heterograft heart valve replacement performed in the United States and the first heterograft heart valve replacement performed in a long-term animal survivor. On April 3, 1965, at the New York Medical College Flower Fifth Avenue Hospital, a sheep aortic valve was implanted into the aortic position in a calf. The animal, which had been growing and thriving, was killed 3 months later. On Friday, July 7, 1967, in a 4.5-hour operation, my colleagues and I replaced a rheumatic stenotic aortic valve of a 38-year-old Greek-American waiter with a calf aortic valve (Fig 1). In both the animal and human operations the formalin-processed valves were sewn in freehand, without stent or sewing rings. When the patient was discharged 3 weeks later, the hospital issued a news release to the lay press.

Beginning in September 1968, we published a series of abstracts and papers documenting our work with aortic and mitral heterografts and homografts in 191 calves and 2 humans [1–5]. For 3 years, beginning in 1965, this work had been supported by US Public Health Service National Institutes of Health Grant 41-318-2, originally submitted in 1964. Until 1965 no report on heterograft valves had been published and we were not aware of work being done elsewhere.

By 1964 it had become clear that mechanical heart valves could save the lives of thousands who would otherwise be lost. Mechanical and coagulation complications following the use of these valves motivated us to search for alternatives. Homografts, the natural choice, would never prove adequate due to lack of supply. Nonhuman animal valves might prove an acceptable alternative. Theoretically, compared with synthetic valves, heterografts offered a more natural substitute, low cost, ready availability and, hopefully, superior hemodynamics, less thrombogenicity, less need for anticoagulants, and fewer associated problems.

Two fundamental questions loomed large. First, could donor rejection be avoided in a recipient from a widely disparate species? Second, could a biologically altered tissue transplant withstand the ceaseless pulsatile pounding inside a beating heart? Should heterografts indeed prove acceptable, would donor valves of one species prove superior to those of another? What if the valves of all domesticated species were truly interchangeable? What were the special problems inherent in the harvesting, preserving, sterilizing, and implanting of these heterografts?

Calves were selected as the universal recipient because of their size and their availability. Three times each week we harvested 20 to 30 calf hearts and 6 L of blood for our heart-lung machine from the abattoirs of New Jersey. Hearts were collected in a sterile plastic sack and handled thereafter with aseptic technique. The valves were carefully trimmed, leaving only a 4- to 5-mm rim of aorta attached. No more than three hours were allowed to elapse between harvesting and processing.

The aortic valves of humans and all domesticated species studied are remarkably similar in structure, differing only in the relative proportion of connective tissue components. Dog and goat valves are too small for adult human use but valves from the calf, hog, and sheep are suitable. On the tensilometer the bursting strength of all valves was nearly identical. Valves from slaughtered domesticated animals, even if taken aseptically one hour postmortem, are contaminated, often heavily. If fresh hearts or aortic valves are stored in nutrient medium at 4°C for as little as eight hours, autolysis of their connective tissue, as seen by the electron microscope, will impair their ability to withstand mechanical stress.

Around 1,200 aortic and pulmonic valves of sheep, goats, hogs, humans, calves, and dogs were harvested and studied grossly and by light and electron microscopy. A pulse duplicator was used to study flow patterns and a tensilometer measured bursting strength. Ethylene oxide and β-propiolactone as sterilizing agents and lyophilization (freeze-drying) as a preservation technique were evaluated and rejected because they weakened the valve. Ten percent formalin (4% formaldehyde) buffered to pH 5 (1) was simple to use and simultaneously preserved and sterilized, (2) provided a safety margin so great that a treated valve could be inoculated with *Clostridia* without becoming infected, (3) abolished the problem of antigenicity because species specificity disappeared (a formalin-treated valve may promote a foreign body reaction, but never rejection), and (4) produced valves that were actually stronger than fresh, untreated valves because collagen cross-linkage was enhanced. Glutaraldehyde is a stronger collagen cross-linking agent and, unlike formaldehyde, the linkages are said to be irreversible.

Why is all this important? Because the histological events that take place in the heterograft valve after implantation determine its success or failure. The critical moieties are the collagen fibers of the donor and the fibroblasts of the recipient. Elastic tissue remains relatively aloof from this process. Upon implantation, the graft collagen fibers begin to degenerate and young immature host fibroblasts [6] are found streaming into the

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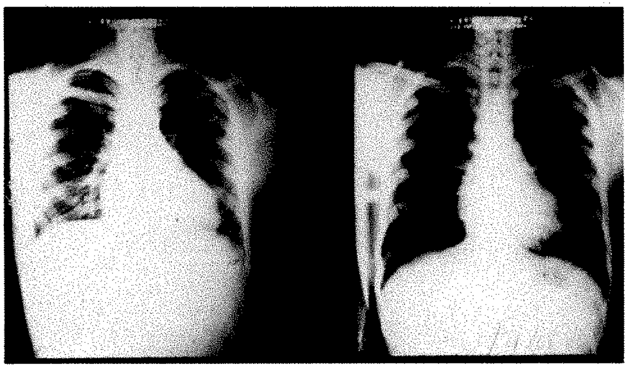

Fig 1. (Left) Posteroanterior chest roentgenogram taken before heterograft aortic valve replacement in January 1967. (Right) Roentgenogram made 6 months after operation.

donor graft in a seemingly purposeful directional manner. These host fibroblasts begin to palisade and lay down new collagen. A dynamic equilibrium is established, with simultaneous breakdown of old and build-up of new connective tissue within the donor valve.

Thus, the graft is a template, an organic stent onto which the recipient, at least partially, recreates a new autologous valve—a phoenix rising anew from its own ashes. A valve heterograft is different from a cloth, metal, and plastic prosthesis. It is truly a graft. Like any graft, a "take" requires intimate, motionless graft-to-host tissue apposition to facilitate the ingress of host cells and tissue regeneration. Mounting frames and sewing rings prevent this and, in the aortic position at least, they are unnecessary because freehand implantation is technically easy.

Early unfavorable short-term results with formalin-fixed valves may only reflect the technical inadequacy of early valve preparation, and later reports of degeneration of glutaraldehyde-fixed valves may be due to the interposed stents and rings.

Heterograft valves are silent, do not cause hemolysis, are relatively nonthrombogenic, and usually do not require anticoagulation. Their major drawback is durability. Although in some centers heterografts remain the valve of choice, in general they are reserved for older patients and those in whom anticoagulation is undesirable. Future progress will be in the development of improved preservation techniques to retard degeneration by collagenase and other proteases, and the adoption of techniques permitting donor–host apposition, cellular ingrowth, and tissue reparation.

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Plastic Surgery for Cardiac Valves: 15 Years' Experience

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We suggest that all patients with heart valve diseases should be considered for reconstructive plastic surgery, regardless of the numerous modern mechanical and biological prostheses available in a cardiac surgeon's arsenal. We have 15 years of experience, with 903 plastic surgical procedures with cardiopulmonary bypass for acquired mitral (636), aortic (51), and tricuspid (216) valve diseases. The 15-year survival rate for patients with mitral stenosis was 68% ± 5%, and the 8-year survival rate for patients with mitral insufficiency was 81% ± 3%. The 10-year survival rate for patients with mitral and tricuspid valve disease was 59% ± 3% because of the initially grave condition of such patients. For the correction of acquired aortic valve disease we advocate a new type of operation: a method of stent plasty of the aortic root with two circular sutures placed on the level of the arch and fibrotic ring. In combination with gradual commissurotomy, parietal resection of leaflets and paracommissural plication are performed. This procedure is an effective method for the plastic reconstruction of the aortic valve, and it provides a good hemodynamic effect.

(Ann Thorac Surg 1989;48:S77–8)

Together with ball prostheses, modern types of disc prostheses with Pyrolite pivoting disks ("EMIKS" and "LIKS"), biological prostheses ("BAKS"), and, lately, bileaflet "CARBONIKS" valves made of Pyrolite have been widely used in the USSR. None of these commercially available artificial prostheses is an ideal valve substitute, despite their high quality and wonderful hemodynamic characteristics.

For this reason, in our Department of Heart Surgery at the National Research Center of Surgery, when treating all patients with valve diseases we first consider the possibility of reconstructive plastic surgery. We have acquired 15 years of experience, with 903 plastic operations for acquired mitral, aortic, and tricuspid valve disease.

Material and Methods

All operations are performed using hypothermic (26° to 28°C) cardiopulmonary bypass with the addition of cold cardioplegia. Six hundred thirty-six patients underwent mitral valve operations; of these, 467 patients underwent operation for mitral valve stenosis and 169, for mitral insufficiency. The operative technique included mitral commissurotomy (598 patients), chordoplasty (124 patients), cuspoplasty (31 patients), and atrioplasty (10 patients). All these methods of mitral valve correction are now commonplace. More interesting is the case of chordoplasty for severe subvalvular stenosis, in which resection of the chordae and, if necessary, their restoration is performed by dissecting the base of one of the leaflets (more often the posterior one), followed by a plasty of this zone with a patch of glutaraldehyde-treated xenopericardium.

Two hundred sixteen patients underwent operation on the tricuspid valve. We consider the technique described by De Vega to be preferable. In patients with severe insufficiency and high pressure in the pulmonary artery we inserted a weight-bearing ring. Lately all operations have been performed using special obturators 33 and 35 mm in diameter.

Plastic surgical procedures on the aortic valve have been performed in 51 patients. The technique used in this operation consists of gradual commissurotomy, parietal resection of the thickened leaflets, and paracommissural plication of leaflets. Quite unique is the method of stabilizing the natural collagenic stent of the aortic root with two circular sutures. One is placed on the level of the fibrotic ring of the aortic root and the other on the level of the arch ring. The thread ends of both sutures are withdrawn outward in the aorta and tightened gradually to achieve the desired pressure gradient and degree of regurgitation (Fig 1).

Results

In the last 200 operations for mitral stenosis the hospital mortality was 1.5%, and in the last 100 operations for mitral insufficiency, 3%. The repair is considered to be a success if the pressure gradient across the mitral valve does not exceed 3 mm Hg and regurgitation does not exceed 7% of stroke volume. The 15-year survival rate in patients with mitral stenosis was 68% ± 5%, and the 8-year survival rate in patients with mitral insufficiency was 81% ± 3%.

For combined mitral and tricuspid valvular diseases the long-term results are worse than for isolated mitral valve repair. This can be explained by the initially grave condition of such patients. The 10-year survival rate is 59% ± 3%.

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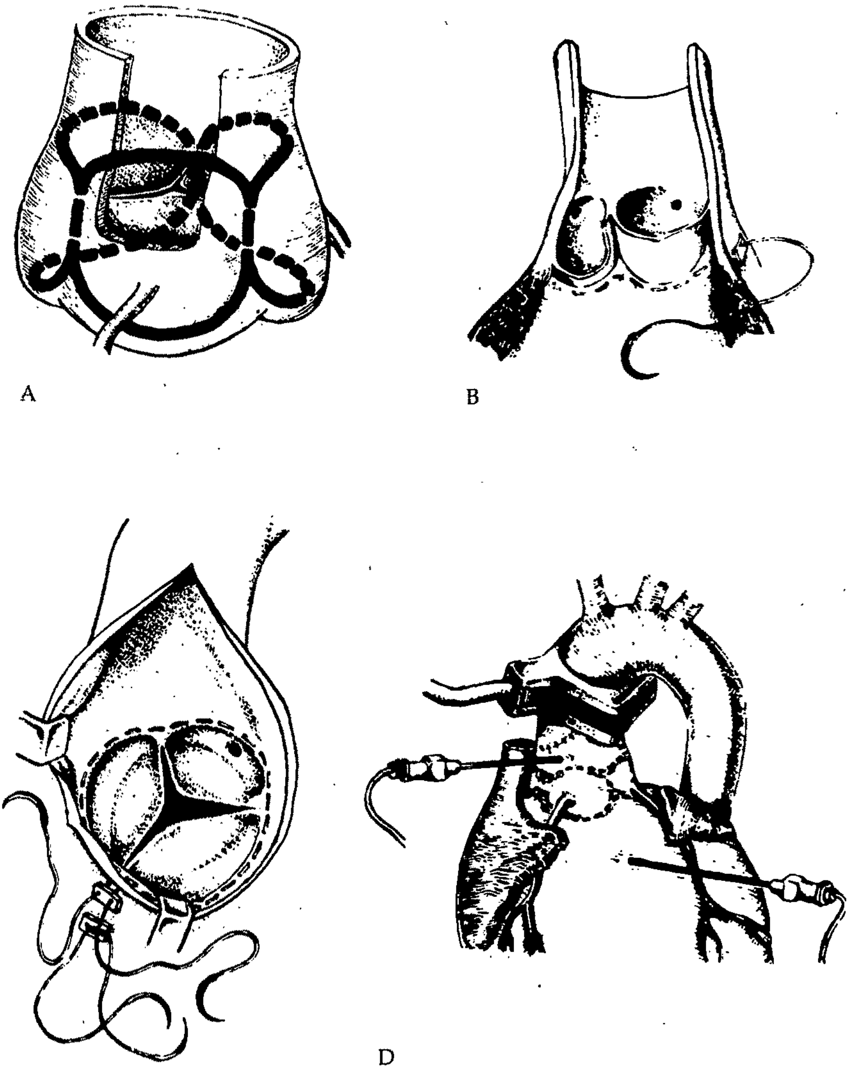

Fig 1. The method of aortal valve stent plasty: (A) natural elastic stent of aortic root; (B) circular suture of fibrotic ring; (C) circular suture of arch ring; and (D) tightening of the sutures and hemodynamic control.

Plastic operations for aortic valve diseases present a new chapter in surgery. Our early results are encouraging. The basic criterion is the hemodynamic adequacy of valvular disease repair: the pressure gradient should not exceed 15 mm Hg, and regurgitation should not be more than 4% to 6%.

Comment

The desire to preserve the patient's proper valve is quite natural. The great diversity of surgical techniques used in plastic surgery for mitral, aortal, and tricuspid valve disease can be accounted for by the large number of anatomical structures that participate in the functioning of the valve. Therefore, modern surgical valvuloplasty is impossible without an exact knowledge of topographic anatomy and an understanding of the functional significance of every anatomical element.

The technique of mitral valve reconstruction has been well developed by Carpentier and colleagues [1]. Today this enables us to consider the possibility of a reconstructive, valve-preserving operation in patients who have mitral valve disease without pronounced calcinosis or signs of active infection if the elements of the chordopapillary apparatus are relatively intact. Only if plastic surgery is impossible should the replacement of the valve be performed.

Our approach to the aortal valvuloplasty is based on morphological and biomechanical research on the structure and function of the aortic root. As a result, we have discovered a natural fiber stent of the aortic root, consisting of the fibrotic ring, arch ring, and commissural rods. This stent acts as a mechanical damper of loads. Together with the aortic sinus and the ascending aorta, which act as hydraulic dampers, this natural stent provides for the long-term function of the aortic valve cusps without regurgitation or a serious pressure gradient. The method of aortic root stent plasty [2] is based on the mechanism of the valve-aortic complex described above and, combined with other surgical techniques, is our method of choice in patients without pronounced calcinosis or rupture of the aortic valve leaflets.

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New Cardiac Bioprostheses: Theory, Experiments, and 10 Years of Clinical Use

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The biological valve "BAKS" has the following specific features: (1) it is practically devoid of immunogenicity due to fermentative-chemical treatment; (2) it is completely treated with glutaraldehyde through gradual soaking in solutions of increasing concentration; (3) the biological part is fashioned taking into account the biomechanics of the aortic root; (4) the polypropylene stent is functional due to the use of the principles of bionics in valve construction; and (5) practically no thromboemboli occur, because of the special morphologic organization of the cuff and the distant location of the bioprosthesis leaflets from the stent edge. In the Department of Heart Surgery of the National Research Center of Surgery, "BAKS" valves have been used in 237 patients undergoing isolated mitral valve replacement for rheumatic heart disease. Of these 35% were younger than 35 years, 93.7% belonged to New York Heart Association functional class IV, and 24% had had a previous heart operation. The 10-year survival rate without hospital mortality was 68.94% ± 4.86%. Total follow-up was 11,232 patient-months (range; 6 to 118 months; mean, 57 months; 97% complete). Main causes of death and reoperation were (per patient-year) infectious endocarditis, 3.2%; spontaneous bioprosthesis degeneration, 0.96%; mechanical dysfunction resulting from damage in the manufacturing of the prosthesis, 0.74%; left atrial thrombosis and/or thromboemboli, 0.5%; sudden death, 0.2%; cardiac insufficiency, 0.3%; and other, 0.4%.

(Ann Thorac Surg 1989;48:S79–80)

In many countries during the last 20 years biological valve prostheses have been thoroughly studied in experiments and in clinical practice. The major advantages of these bioprostheses (central flow, good hemodynamic characteristics, low risk of thromboemboli) and also their drawbacks (growing risk of dysfunction 5 to 7 years after operation and the especially high risk of dysfunction in young patients) are now clearly identified. All modern efforts to develop a new generation of bioprostheses are aimed at decreasing the risk of calcification and based on investigations of the reasons for this pathological process.

At the Department of Heart Surgery of our Center we started work on the development of the "BAKS" bioprosthesis in 1976. After 3 years of experiments, in 1979, the first implantation of "BAKS" in a patient was performed. Over the past 10 years we have implanted 237 xenobioprostheses for isolated rheumatic disease of the mitral valve [1].

Material and Methods

"BAKS" is made of a porcine valve–aortic complex. After the biological material is delivered to the laboratory it is subjected to complex fermentative and chemical treatment. Such treatment ensures (1) the complete destruction of those cells in the leaflets that are the main carriers of antigenic activity and also the zones of high calcium content; (2) the elimination of water-soluble proteins and products of fermentative hydrolysis; (3) complete restructuring as a result of 30-day soaking in solutions of glutaraldehyde of increasing concentrations (up to 0.5%).

The immunogenicity of the obtained biomaterial was studied according to the "second set" method in experiments on inbred rats. This biomaterial was compared with native biomaterial and other methods of xenovalve treatment. Structural stability was studied through differential thermical analysis with the device "Setaram" (France). The mechanical properties of the biological tissue before and after treatment were tested with the device "Instron-1122" (England).

The fashioning of the biological part of the prosthesis, the creation of the functionally supporting stent from propylene, and the principles of manufacture were based on a morphological and biomechanical study of aortic root elements.

The hydraulic characteristics of "BAKS" have been compared with those of other biological and mechanical cardiac-valve prostheses in a mock circulatory system with both continuous and pulsatile flow.

"BAKS" implantation in the supraannular position was performed using cardiopulmonary bypass with cold cardioplegia. Of the 237 patients, 93.7% belonged to the New York Heart Association functional class IV and 35% were younger than 35 years. A total of 57.4% had mitral valve calcinosis and 16% had left atrial thrombosis and thromboemboli in their medical history.

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We studied the morphology of 37 bioprostheses removed from several days to 9 years after implantation.

Results

Immunological investigations in experimental and morphological studies of removed "BAKS" prostheses demonstrated that the fermentative-chemical method permits one to obtain bioprostheses practically void of immunogenicity. In the valve–aortal complex of animals and humans a clear topography of fiber structures has been discovered: collagen fibers are distributed mostly in the fibrotic ring of aortic root bases, commissural rods, and the arch ring. Comparative analysis of these data and the results of hemodynamic and biomechanical studies demonstrated that these elements form a natural elastic stent of aortic root, which performs a weight-bearing function for the aorta, sinus of Valsalva, and leaflets. The construction of "BAKS" preserves the function of all elements of the aortic root and provides the bioprosthesis with hemodynamic properties similar to those of the natural organ; the mean pressure gradient in bioprostheses is 4.32 ± 0.36 mm Hg (range, 2 to 9 mm Hg), with practically no regurgitation.

The 10-year survival rate without hospital mortality was 68.9% ± 4.86%. Total follow-up was 11,232 patient-months (range, 6–118 months; mean, 57 months; 97% complete). In the late postoperative period 23 patients died without reoperation. Thirty-seven patients underwent a second operation; of these operations 25 were successful. The main causes of mortality and bioprosthesis dysfunction (per patient-year) were: infectious endocarditis, 3.2%; spontaneous bioprosthesis degeneration, 0.96%; mechanical dysfunction resulting from damage in the manufacture of the prosthesis, 0.74%; left atrial thrombosis and/or thromboemboli, 0.5%; sudden death, 0.2%; cardiac insufficiency, 0.3%; and other, 0.4%.

Morphological studies demonstrated the gradual impregnation of bioprosthesis tissue with recipient plasma proteins starting from the first postimplantation day.

Comment

Our experimental research was aimed at developing a bioprosthesis with high biological and mechanical durability. We consider the construction of "BAKS" as capable of sustaining long-term mechanical loads so that its initial functional properties are not destroyed and do not deteriorate over time; also, the biological part of this bioprosthesis resists biologically destructive factors. Many of the problems have been solved. The number of dysfunctions resulting from the spontaneous degeneration of leaflets (without infectious endocarditis) is not high. The major problem that should be solved with the development of a new generation of bioprostheses is the impregnation of leaflets with recipient plasma proteins. In our opinion, this process, together with the mechanical loads that lead to the destruction of the density of fiber structures, accounts for spontaneous collagenic degeneration and bioprosthesis calcification. In patients with infectious endocarditis this process occurs at a more rapid rate.

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The Hancock Modified-Orifice Porcine Bioprosthetic Valve: 1976–1988

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The Hancock modified-orifice porcine valve was fabricated as a result of documented obstruction of the Hancock standard porcine valve in small sizes related to the retained muscle bar of the right coronary cusp. We implanted the first clinical Hancock modified-orifice valve in 1976, and have used this valve for aortic valve replacement to the present time. This analysis compares and contrasts the clinical performance of 401 Hancock standard and 385 Hancock modified-orifice valves over a period of 10 years. Statistical significance in actuarial curves at 120 months was noted in long-term survival and thromboemboli. There was a slightly smaller amount of structural valve degeneration and incidence of reoperation with the modified-orifice valve compared with the standard valve. The Hancock modified-orifice valve has proven to be a satisfactory aortic valve replacement device, and its complex fabrication has withstood the test of time.

(Ann Thorac Surg 1989;48:S81–2)

In the early 1970s, after the successful introduction of the Hancock porcine bioprosthetic valve in 1970 [1], reports began to appear about serious transvalvar obstruction in the smaller (25-mm diameter) sizes of aortic porcine valves [2]. The Hancock valve company then devised a technique to modify and improve the effective valve orifice in the small porcine valves by removing the native right coronary cusp, which contains a bar of ventricular muscle despite careful trimming and thinning during mounting of the native porcine valve, and substituting the noncoronary cusp from a second animal, leaving a relatively nonobstructive effective orifice with cusps opening completely (Fig 1). Obviously, concern arose over the possibility of increased structural valve degeneration because of the more complex fabrication process. We implanted the first clinical Hancock modified-orifice (HMO) valve in the world in 1976 and have continuously used this valve through 1988 as an aortic valve replacement device in properly selected patients.

This paper analyzes our experience with the HMO valve and contrasts its performance with the Hancock standard valve (HSV) at our institution, updating a previous report [3].

Material and Methods

Data analysis was carried out for 385 patients with HMO aortic valves inserted from October 1976 to January 1988 and 401 patients with HSVs inserted from January 1972 to January 1988. Demographic data and information on associated pathology are summarized in Table 1.

Table 1. Demographic and Pathological Data for Patients Studied

Variable	HSV (n = 401)	HMO (n = 385)	*p*
M/F	322/79	257/128	0.001
Mean age (yr)	59	64	0.0001
AS/AR	246/155	302/84	0.001
Functional class			
I	2	2	
II	24	22	
III	232	265	
IV	143	96	
Associated CABG	94–401 (23%)	131/385 (34%)	0.0001

AR = aortic regurgitation; AS = aortic stenosis; CABG = coronary artery bypass grafting; HMO = Hancock modified-orifice valve; HSV = Hancock standard valve.

One can glean slight differences in the demography of patients from our data. In the HMO group patients tended to be female and older and had more aortic stenosis and coronary artery disease requiring smaller valves and a higher rate of concomitant coronary artery bypass grafting. Operative techniques were similar and performed by the same surgeons with previously de-

Table 2. Follow-up, Mortality, and Morbidity Data

Variable	HSV	HMO	*p*
Operative mortality	27/401 (7%)	9/385 (2.3%)	0.004
Mean postop follow-up (mo)	84	65	. . .
LTFU	3%	5%	NS
Late deaths	147	74	0.001
Structural valve dysfunction	46	22	0.002

HMO = Hancock modified-orifice valve; HSV = Hancock standard valve; LTFU = lost to follow-up.

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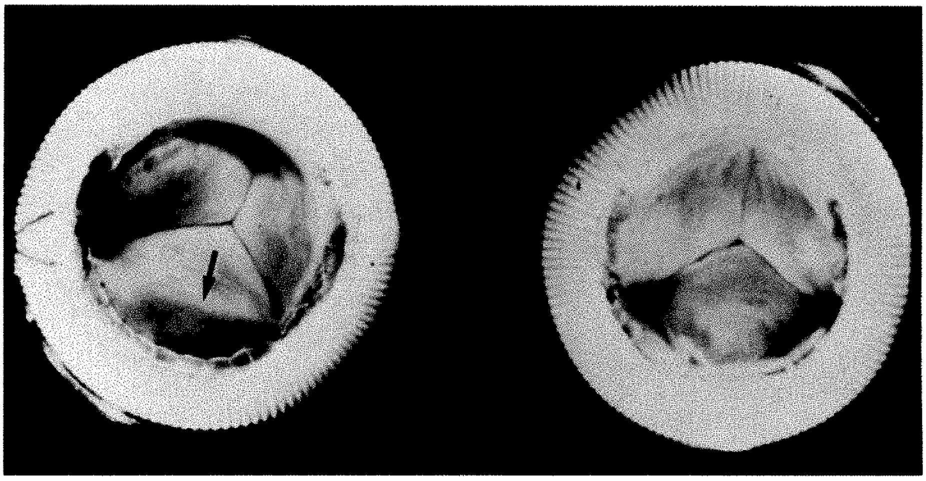

Fig 1. (Left) Standard porcine valve. Arrow *points to muscle bar at base of noncoronary cusp. (Right) Modified-Orifice valve without muscle bar. (Reproduced from DiSesa VJ, Allred EN, Kowalker W, Shemin RJ, Collins JJ Jr, Cohn LH. Performance of a fabricated trileaflet porcine bioprosthesis. J Thorac Cardiovasc Surg 1987;94:220, by permission of The C.V. Mosby Co.)*

scribed techniques [4]. No valve was less than 21 mm in diameter in either group, but the percentage of 21-mm valves was higher in the HMO group (*n* = 140). Coumadin (crystalline warfarin sodium) was not given to any patient postoperatively unless he or she was in atrial fibrillation. Follow-up was taken by personal exam or telephone interviews on or about October 1, 1988. The percent lost to follow-up was 3% for the HSV group and 5% for the HMO group. All data were entered into the Harvard School of Public Health mainframe computer (Digital), and BMDL and SAS packages were used to calculate statistical significance by univariate, multivariate, and actuarial analysis.

Results

The operative and late results of aortic valve replacement with the HSV or HMO valve are summarized in Tables 2 and 3. The higher operative mortality in the HSV group may be due to earlier time of performance and higher percentage of patients with aortic regurgitation. On the other hand, virtually all patients with HMO valves had crystalloid cardioplegia (introduced in early 1977), and this group had more patients with predominantly aortic stenosis, but also exhibited a higher incidence of coronary artery disease requiring concomitant coronary artery bypass.

Table 3. Probability of Freedom From Risk Events at 10 Years

	Probability of Freedom From Event 10 Years Postoperatively (%)		
Event	HSV (n = 106)[a]	HMO (n = 91)[a]	*p*
Death (excluding operative death)	56 ± 3[b]	65 ± 4	0.017
Thromboemboli	88 ± 2	80 ± 4	0.006
Anticoagulant-related hemorrhage	97 ± 1	94 ± 3	NS
Hemolysis	100	99 ± 1	NS
Structural valve dysfunction	81 ± 3	83 ± 4	NS
Infection	94 ± 1	94 ± 2	NS
Reoperation	79 ± 3	84 ± 4	NS
All morbidity	63 ± 3	55 ± 5	0.08

[a] Number of patients at risk at 10 years. [b] Standard error of the mean.

HMO = Hancock modified orifice valve; HSV = Hancock standard valve.

The higher incidence of structural valve degeneration in the HSV group possibly reflects a longer follow-up, although the actuarial analysis at 10 years also suggests slightly better durability in the HMO valve.

In Table 3 are summarized the actuarial calculations of probability of freedom from risk events at 10 years in both series. There is no increased incidence of structural valve degeneration for the HMO valve, and in fact there appears to be a slightly lower incidence of this complication than with the standard Hancock valve, which validates the fabrication technique of the HMO valve. There is a slightly higher incidence of thromboemboli, which may reflect the smaller valves used, but these were not emboli leaving any sequelae. Finally the incidence of reoperation is also lower with the HMO valve, reflecting the lower incidence of structural valve degeneration.

In conclusion, the HMO valve offers excellent relief of symptoms of aortic stenosis and aortic regurgitation. The more complex fabrication process does not affect the long-term durability of the valve, and its continued use for aortic valve replacement, particularly in the small aortic root in the elderly, seems justified.

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Actuarial Analysis of a Uniform and Reliable Preservation Method for Viable Heart Valve Allografts

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CryoLife has developed a method for cryopreserving allograft heart valves for transplantation. Since 1984, 6,907 valves have been processed and 4,216 transplanted. Documentation was available on 2,647 transplants, 11 of which were removed for structural deterioration and 13, for nonstructural deterioration. At the end of 35 months, actuarial survival was 99.17% and the estimated freedom from reoperation, 97.16%. There have been no reports of thromboembolism or valve-related death.

(Ann Thorac Surg 1989;48:S83–4)

The allotransplantation of heart valves was pioneered in 1955 by Gordon Murray with a series of fresh aortic valve transplants. In 1962, Mr Donald Ross [1] and Sir Brian Barratt-Boyes and colleagues [2] independently performed the first orthotopic transplantations of allograft aortic valves. Because of the limited supply of transplantable tissue and the short periods of tolerable tissue ischemia, methods of extended storage were used including cold storage in tissue culture media with antibiotics, freeze drying, and freezing. Although the initial studies did not examine cell viability, subsequent work by O'Brien and associates [3] suggested that the viable components of the allograft enhance long-term survival. The 92% freedom from valve-related complications at 6 years reported by O'Brien and co-workers [3] is particularly impressive when compared with the 73% freedom for nonviable homografts, the 65% freedom for mechanical valves, and the 57% freedom for bioprostheses.

Material and Methods

Since 1984, 4,397 human hearts have been received from 176 independent procurement centers. Of the 6,907 valves processed, an estimated 4,216 have been transplanted by 350 physicians at more than 200 centers throughout the United States and Canada and three centers in Western Europe, for a total of 4,478 transplant-years. Documentation was available on 2,647 of the transplanted valves.

The primary cause for valve transplantation was as follows: rheumatic fever, 3%; degenerative disease of the aortic or pulmonary valve, 10%; preexisting endocarditis, 4%; congenital disease of the aortic valve, 11%, and of the pulmonary valve, 55%; hypoplastic left heart, 3%; and replacement of a previous prosthetic valve or conduit, 12%. The homograft was used for the right heart in 63% of the patients and the left heart in the remaining 37%.

Technique

Successful maintenance of cell viability during processing is dependent on a number of variables, which have previously been discussed in detail [4]. On arrival at the processing laboratory, the hearts were dissected and the valves placed into antibiotic media optimized for minimum cytotoxicity. Then the valves were transferred to a cryoprotective solution containing dimethylsulfoxide and cryopreserved in liquid nitrogen. After thawing and dilution, cell survival of approximately 90% was obtained for the fibroblasts of the cryopreserved valve leaflets relative to untreated fresh controls [5].

Statistical Method

Implant data were grouped into 1-month intervals and analyzed according to the life-table methods described by Cox and Oakes [6].

Results

Of the 2,647 transplants on which data are available, 11 have been removed because of structural deterioration (Table 1). Calcification, prevalent with bioprosthetic implants, has been reported in only four instances. These were restricted to younger recipients (mean age, 1.4 years), and occurred within a mean time of 1.4 years. The number of removals resulting from calcification was remarkably low considering that 53% of all transplants are in children less than 10 years old. Cusp degeneration (three instances), dehiscence (two), and insufficiency/regurgitation (two) accounted for the remaining seven removals for structural deterioration. At the end of 35 months, actuarial survival was 99.17%.

Nonstructural deterioration (13 instances) is summarized in Table 1. By definition, this means instances when the valve was removed for reasons not directly attributable to the valve, such as preexisting suture lines, Dacron conduit extensions, and surgical technique. An additional 5 valves were removed because of unsuccessful treatment of preexisting valve endocarditis.

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Table 1. Summary of Data on Removal of Allografts

Cause	No. of Valves	Mean Time of Implantation (yr)	Mean Age (yr)	Right Heart (%)	Left Heart (%)	Comment
Structural deterioration						
Calcification	4	1.4	1.4	75	25	Children
Cusp degeneration	3	0.6	43	33	66	Procurement time > 24 h (2); immunology (2)
Dehiscence	2	0.1	38	0	100	Hypertensive (1); preexisting endocarditis (1)
Insufficiency/regurgitation	2	0.6	33	0	100	Preexisting endocarditis (1)
Total/mean	11	0.7	29	36 (4/11)	64 (7/11)	
Nonstructural deterioration						
Calcification	2	1.4	7	100	0	Dacron conduit extension (1); preexisting suture (1)
Stenosis	5	1.3	16	80	20	Dacron conduit extension (3); preexisting suture (1)
Torn valve/conduit	2	0.0	60	0	100	Intraaortic balloon pump (2)
Insufficiency/regurgitation	2	0.9	25	50	50	Technique (2)
Miscellaneous	2	0.9	7	100	0	Conduit twist (1); associated patch aneurysm (1)
Total/mean	13	0.9	23	69 (9/13)	31 (4/13)	

At 35 months, the combined total of 29 removals representing all reoperations resulted in an actuarial survival of 97.16% (Fig 1).

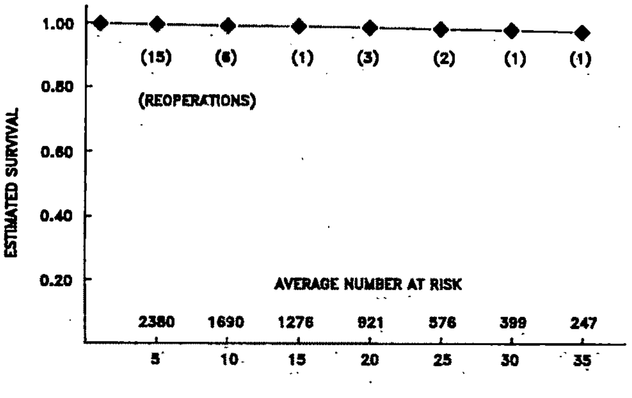

Fig 1. All 29 removals were used to generate this curve for actuarial survival without reoperation. At the end of 35 months, the estimated freedom from reoperation for a cryopreserved allograft valve is 97.16%.

Comment

Actuarial survival analysis of an estimated 4,478 implant-years of data suggests that cryopreserved allograft heart valves are superior in performance compared with prosthetic and bioprosthetic tissue implants.

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Cryopreserved Valve Conduits for Outflow Tract Reconstruction in Pediatric Patients

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One hundred twenty-one cryopreserved pulmonary and aortic allograft valves and conduits have been implanted over the past 4 years to reconstruct complex outflow tract anomalies. Their versatility, relative ease of implantation, and ability to provide a surgical option in patients with an otherwise inoperable condition make these allografts invaluable to the pediatric cardiac surgeon.

Material and Methods

Right Ventricular Outflow Tract

Eighty-nine children underwent operation to reconstruct the right ventricular outflow tract. Seventeen repairs using aortic allografts represent the early experience with use of cryopreserved valves. Unless anatomy dictates the use of the longer conduit of an aortic allograft, pulmonary conduits exclusively are now used for right ventricular outflow tract reconstruction.

The 89 patients who underwent aortic or pulmonary reconstruction of the right ventricular outflow tract ranged in age from 1 week to 16 years (mean age, 3.2 years). Diagnoses were tetralogy of Fallot in 41 patients, pulmonary atresia in 16, truncus arteriosus in 9, double-outlet ventricle in 9, transposition of the great arteries in 8, and pulmonary stenosis in 6. Seventy-four children (83%) had had 79 prior cardiac surgical procedures including 37 unilateral and eight bilateral systemic–pulmonary artery (PA) shunts.

The allografts implanted had an internal diameter ranging from 9 to 26 mm (mean internal diameter, 20 mm). Sixty-eight children (76%) received allografts of acceptable adult size [1].

There were 19 perioperative deaths (21%). Fourteen were attributed to low cardiac output. Other causes included sepsis, pulmonary vascular disease, pneumonia, and arrhythmias. Two late deaths occurred, one secondary to neurological problems and the other secondary to pulmonary problems.

A 12-year-old patient received concurrent pulmonary and aortic valve allografts. At age 5 years, he had a Rastelli procedure employing a porcine valved conduit. Aortic insufficiency and conduit stenosis subsequently developed. The allograft procedure was successful and at 18 months' follow-up, the patient is asymptomatic.

One pulmonary allograft was replaced because of insufficiency 15 months after the initial operation to repair tetralogy of Fallot. At reoperation, the left PA was stenotic. A replacement pulmonary allograft including the PA bifurcation was inserted, and the child continues to do well 2 years after reoperation. All 57 surviving children are asymptomatic with functioning valves after 1 month to 44 months of follow-up (mean follow up, 20 months).

Primary pulmonary allograft valved conduit repair of tetralogy of Fallot offers the most complete restoration of structure and function currently possible. In an isolated study [2], 12 patients who underwent pulmonary artery conduit repair of simple tetralogy of Fallot were compared with a chronologically overlapping group of 25 patients who received transannular patch repair of the same disease. The incidence of both early postoperative right ventricular failure (17/25 or 68% versus 2/12 or 17%) and hospital death (6/25 or 24% versus 1/12 or 8%) was noticeably greater in the transannular patch group. Of the patients who had initial transannular patch repair, 5 subsequently required reoperation to receive a pulmonary valve allograft. These children as well as the 11 survivors in the pulmonary artery conduit repair group are asymptomatic with mild pulmonary regurgitation, which has not progressed. Although not clearly superior, early clinical results with primary placement of a pulmonary artery conduit are at least comparable with those with transannular patch repair.

Left Ventricular Outflow Tract

Since February 1985, 32 aortic valve allografts have been used to reconstruct the left ventricular outflow tract. This experience includes 21 extended aortic root replacements [3], seven other aortic root replacements, one free-sewn allograft, and three miscellaneous left ventricular outflow tract reconstructive procedures.

Twenty-one extended aortic root replacements were performed in 20 children. Patient age ranged from 11 days to 15 years (mean age, 7 years). Twenty-one patients had undergone 30 prior cardiac procedures. The majority were aortic subvalvular membrane resections, aortic valvotomies, and aortic coarctation repairs. Indication for operation was recurrent subvalvular aortic stenosis in 12 patients, aortic stenosis with hypoplastic annulus in 4, and complex aortic stenosis in 3. Two children had severe aortic insufficiency, 1 secondary to endocarditis and 1 secondary to aortic allograft valve failure.

Aortic valve allografts ranging from 11 to 23 mm in

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internal diameter (mean internal diameter, 19 mm) were placed. There was one intraoperative death (5%), an 11-day-old infant with severe aortic stenosis after aortic valvotomy at birth. Extensive endocardial fibroelastosis of the entire left ventricle was found, and the patient could not be weaned from cardiopulmonary bypass. Complications included three incidences of transient heart block. The most serious complication was *Serratia marcescens* mediastinitis, which resolved with no allograft damage. Eight patients had no perioperative problems, and all postoperative complications were resolved by the time of hospital discharge.

In a 22-month-old child, severe aortic regurgitation developed 8 months after extended aortic root replacement. Surgical findings were compatible with rejection, and a regimen of cyclosporine was begun with implantation of the second allograft. Two months after redo extended aortic root replacement, the child is doing extremely well. Early follow-up (mean period, 19 months) reveals the remaining patients are asymptomatic.

Seven additional aortic root replacements were performed in patients with a variety of complex lesions. Five patients (71%) had undergone a previous cardiac procedure. There were two perioperative deaths, one secondary to *Candida* sepsis in a patient with Shone's anomaly who had mitral valve replacement in addition to aortic root replacement. The second death occurred as a result of myocardial dysfunction in a newborn seen with aortic stenosis, insufficiency, and interrupted aortic arch. There was one late death. The patient was seen as a neonate with aortic root and valvular hypoplasia. Three successive allografts were inserted when the patient was 3 days, 2 months, and 4 months old. The allografts became insufficient, and rejection was suspected. Azathioprine therapy was instituted after the third procedure, but the child died at 1 year of age of irreversible myocardial failure secondary to an infectious cardiomyopathy.

Excellent results were obtained with aortic root replacement in a 2-year-old child with interrupted aortic arch, small aortic annulus and root, and ventricular septal defect. As a neonate, he underwent PA banding and construction of a conduit from the main PA to the descending thoracic aorta. Two years later, he exhibited cyanosis and shortness of breath. At repair, the graft conduit was taken down and the PA band was resected and reanastomosed. The small ascending aorta was detached, closed below the coronary arteries, and anastomosed side-to-side to a long aortic valve allograft used to create a new left ventricular outflow tract. Plication of the left hemidiaphragm was required 2 weeks postoperatively, and supraventricular tachycardia and a decreased level of consciousness were transient problems. The child is active and asymptomatic 6 months after operation.

Comment

The advantages of cryopreserved pulmonary and aortic allograft valves and conduits over mechanical and other tissue valves are becoming increasingly apparent. The ability to repair very complex lesions, place adult-sized valves in small children, and avoid anticoagulation in the pediatric population offers definite advantages. The early results in these patients with extremely complex cardiac disease encourage the continued use of allograft valve conduits.

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The Intact Bioprosthesis: The First 4 Years

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The Intact porcine bioprosthesis became available for clinical use in 1984. The device incorporates three innovations aimed at reducing calcification and improving durability. Between October 1984 and March 1988, 221 valves were implanted in 200 patients. Sixty-two valves were implanted in the aortic position, 155 valves in the mitral position, and 4 valves in the tricuspid position. The average age was 39 years, and 27 patients were under the age of 20 years. The hospital mortality was 4.5%. The follow-up was from 6 to 48 months, and the actuarial survival at 48 months was 83%. In the group aged less than 20 years six valves have been explanted for calcific prosthetic stenosis. In the group older than 20 years postoperative catheterization studies have demonstrated satisfactory hemodynamics; in this group the results of valve replacement using the Intact valve are regarded as encouraging.

(Ann Thorac Surg 1989;48:S87–8)

The Intact valve is a second-generation porcine valve and incorporates three innovations aimed at improving durability and reducing the potential for mineralization. The valve is mounted on a high-profile stent with deeply excavated sinuses. The high profile retains the natural position of the valve and preserves normal coaptation of the valve cusps. Deep excavation of the sinuses prevents cusp abrasion on the stent rails. The valve is fixed in glutaraldehyde in the semiopen position in a stress-free environment. This method retains the natural structural characteristics of the valve; retention of the crimp pattern of the fibrosa layer of the cusps is thought to be of particular importance in extending durability [1]. The valve is exposed to toluidine blue, which occupies the calcium binding sites; this process should mitigate mineralization. These theoretical advantages encouraged us to embark on a program of valve replacement using the Intact valve.

Clinical Material

During the period October 1984 to March 1988, 221 valves were implanted in 200 patients. The most common operation was isolated mitral valve replacement (Table 1), and the most common indication for operation was chronic rheumatic valve disease (Table 2). Survivors were followed for 6 to 48 months for a total follow-up of 345 patient years. Follow-up is 98% complete.

Results

Table 1. Valve Sizes Used in Each Position

	Valve Size						
Position	21	23	25	27	29	31	33
Mitral	...	...	3	14	45	86	7
Aortic	1	26	20	15	...	...	...
Tricuspid	...	...	...	1	...	1	2

There were nine hospital deaths (mortality, 4.5%). Two of these deaths were related to ventricular perforation, a well-recorded complication of mitral valve replacement using stent-mounted valves [2]. None of the other deaths was valve related. Twenty-four deaths have been recorded during the 48-month follow-up period. Four of the deaths are regarded as valve related. One patient died after a cerebral embolus, 1 patient died because of an anticoagulant-related hemorrhage, and 2 patients died as a result of prosthetic stenosis. The actuarial survival at 48 months is 83%.

Emboli

Three emboli were nonfatal, and one was fatal. The fatal embolus occurred 18 months after the operation.

Paravalvular Leaks

Three patients required reoperation for paravalvular leaks. In 2 of these patients the leak was related to ongoing infective endocarditis.

Functional Class

The functional class of survivors was estimated 3 to 6 months after operation. Two patients were assessed as in

Table 2. Reasons for Valve Replacement

Reason	Percentage of Replacements
Rheumatic valve disease	61
Previous procedure	18
Infective endocarditis	7
Degenerative	12
Congenital/traumatic	2

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New York Heart Association functional class III, and the remainder are in class I or II.

Reoperation

Ten patients underwent reoperation. Three reoperations were related to paravalvular leaks, six to valve calcification, and one to a dissecting aneurysm of the aorta. The actuarial freedom from reoperation at 4 years is 91%.

Patients Less Than 20 Years of Age

Twenty-six patients were less than 20 years of age. In this group six valves have been explanted for calcification. The valves were explanted between 20 and 40 months postoperatively, and actuarial prediction of freedom from calcification at 40 months is 66%.

Postoperative Studies

Twenty-five patients have been restudied. Six of these patients were found to have prosthetic calcification, and all of these valves have been explanted. Four aortic valves were found to have acceptable gradients. In 15 patients in whom mitral valve replacement was performed the gradients across the valves were acceptable in the size 29 and 31 valves. In the smaller valves the gradients were regarded as too high.

Comment

In the group aged less than 20 years results have been disappointing. Six valves have been found to be stenotic as a consequence of calcification. All six of these valves have been explanted, and 1 patient died after reoperation. We no longer implant this device in young patients. In the adult group in whom the larger valves have been implanted the systolic gradients across the aortic valves and mean diastolic gradients across the mitral valves are within the range usually accepted for porcine valves. There has been one episode of primary valve failure in this group. All survivors in this group are currently in functional class I or II, and the results are regarded as encouraging.

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Twenty-Year Comparison of the Human Allograft and Porcine Xenograft

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This study compares a retrospective consecutive series of human allografts and concurrent porcine xenografts implanted over a 10-year interval. There were 571 allograft valves and 1,351 xenograft valves implanted in the aortic and mitral position with mean follow-up of 12.8 years for the allografts and 6.2 years for the xenografts. This study compares the incidence of structural deterioration over long-term follow-up. We found that there was no significant difference between four manufacturers of porcine xenografts, in spite of substantial differences in processing techniques. We found that there was a significant difference in allografts that were premounted on stents as compared with allografts that were not premounted on stents for aortic valve replacement. We found that there was no significant difference between allografts for aortic valve replacement that were not premounted on stents and porcine xenografts implanted in the aortic position. These findings are in marked contrast to those of other reported series with the use of allograft valves.

(Ann Thorac Surg 1989;48:S89–90)

The resurgence of interest in the use of allografts for aortic valve replacement, particularly in young patients, has prompted a comparison of the incidence of sterile structural deterioration in 1,922 patients, 571 allograft and 1,351 xenograft aortic and mitral valve recipients, between 1969 and the present. There was a total of 10,821 patient-years of follow-up in this group, with a follow-up of 82.5% and 89.8%, respectively, and a mean follow-up of 12.8 and 6.2 years, respectively, for the allograft and xenograft patient groups.

Allograft implants were antibiotic-sterilized fresh or frozen viable grafts. Porcine xenografts were obtained from four different manufacturers (Cutter, Hancock, Angell-Shiley, and Carpentier-Edwards xenografts) (Fig 1). All four manufacturers used glutaraldehyde as the basic tanning agent, although with widely varying techniques including glutaraldehyde concentrations from 0.2% to 0.67%, fixation pressures of 0 to 120 mm Hg, and stents composed of metal, polypropylene, and Delrin.

Sterile structural deterioration was the most serious complication analyzed. This occurred predominantly as a result of calcification in both valve types, despite this being an uncommonly reported failure mode in other allograft series. There was no difference in the incidence of structural deterioration relative to the porcine valve manufacturers, which suggests that calcification as a primary mode of valve failure is independent of stent design, concentration of glutaraldehyde, and fixation pressure.

The Angell-Shiley design for increased durability, with 140 anatomically shaped stents, had no effect on structural deterioration. The valve has been modified to the Angell-Duran valve using similar proven materials and methods (Bravo Cardiovascular, Inc, Irvine, CA). Sixty implants have confirmed the proven flow characteristics. There were no differences relative to the experience of the manufacturer as evidenced by the early Cutter xenograft valve, implanted in the early 1970s, and the Carpentier-Edwards valve implanted 10 years later. The allograft valve tended toward earlier structural deterioration than the xenograft in all subgroups (Table 1). Those subgroups that exhibited a significant difference, and the interval during which the deterioration rate reached statistical significance, are outlined in Figure 2. The age of the recipient affected the mean time to structural deterioration in all xenografts and in the mounted allograft series.

It is generally accepted that the fresh antibiotic-sterilized or frozen viable allograft is more durable than the porcine xenograft. These data do not support this thesis. In fact, the data suggest that the stented allograft tissue valve is less durable than the unstented, and raise the possibility of improved durability of unstented xenografts.

The conclusions that we draw from this analysis are as follows. (1) Within a follow-up interval of up to 14 years, the porcine xenografts did not have an increased rate of

Table 1. Time to 40% Valve Failure

Subgroup	Time to 40% Failure (yr)
Porcine aortic valve	12.5
Allograft unmounted aortic valve	11.5
Allograft mounted aortic valve	6.5

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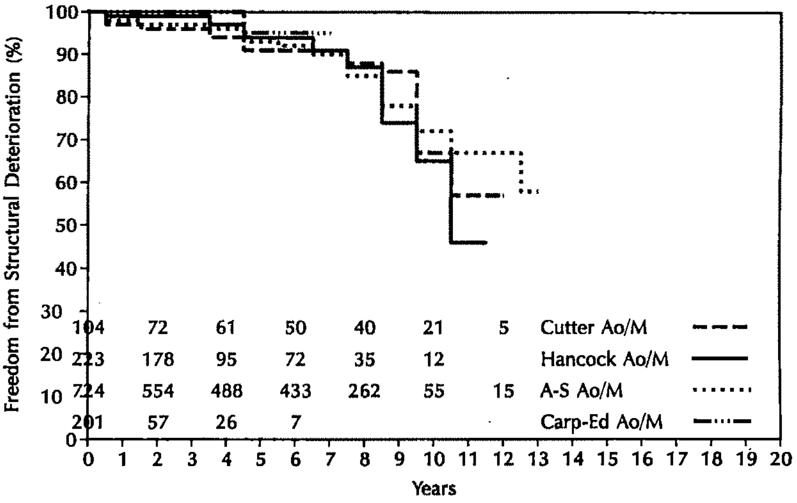

Fig 1. Structural deterioration in porcine xenografts obtained from four different manufacturers with different methods of glutaraldehyde fixation and stent design. (Ao/M = *aortic, stent-mounted;* A-S = *Angell-Shiley.)*

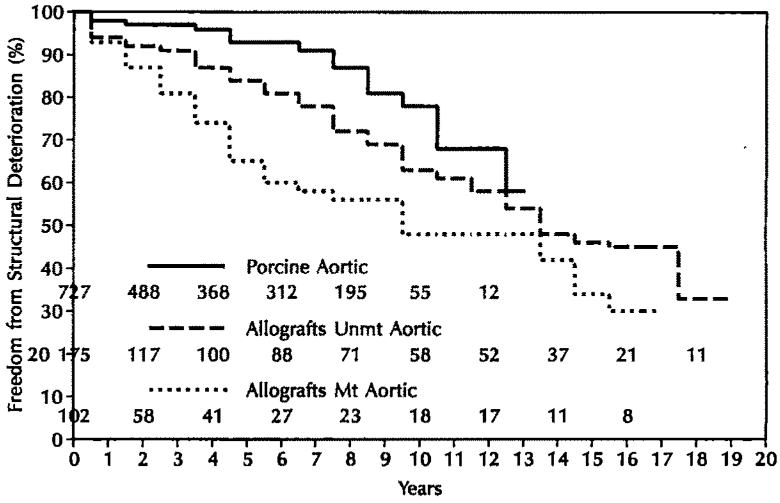

Fig 2. Structural deterioration comparing porcine valves with stent-mounted (Mt) *and non-stent–mounted* (Unmt) *allografts.*

sterile structural deterioration when compared with allografts. (2) Porcine xenograft valves did not have a different rate of structural deterioration relative to manufacturer, in spite of marked differences in stent composition, glutaraldehyde concentration, pressure of fixation, and time of implantation. (3) Stent mounting decreased the durability of aortic allografts. (4) The rate of structural deterioration with porcine valves and with mounted aortic allografts was age-related.

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Technical Problems in Mitral Valve Repair and Replacement

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Operations for mitral stenosis were the earliest successful intracardiac procedures [1]. The first direct attack on the lesion was made in 1923 by Cutler and Levine [2] of Boston. These surgeons introduced instruments and a special punch into the mitral valve with the hope of relieving mitral stenosis. Souttar [3] of London is often credited with the first successful mitral valvotomy, but review of his report strongly suggests that he only explored digitally for mitral regurgitation. No apparent effort was made to pursue further the surgical treatment of mitral valve disease until the late 1940s. Then three pioneers in cardiac surgery, Bailey [4] of Philadelphia, Harken [5] of Boston, and Brock [6] of London, reported success in mitral valve procedures, mitral commissurotomy, valvuloplasty, and valvotomy. Results of closed valvotomy were strikingly improved with the later introduction of expanding valve dilators. Even today, mitral valvotomy by transventricular dilation is used effectively, mostly in Third World countries. Mitral valvuloplasty for regurgitant valves attempted before the availability of cardiopulmonary bypass was ineffective.

With the advent of cardiopulmonary bypass, open repair of mitral stenosis became routine. Now the fused commissures characteristic of rheumatic valvulitis can be incised precisely under direct vision and opening them produces an almost normal, functioning valve. Subvalvular dissection of fused chordae tendineae and papillary muscles enhances the repair. The open technique also permits careful removal of left atrial thrombi, which are frequently present, thus preventing systemic emboli. Even in the presence of valve calcification, repair can be successful. In severely calcified and deformed valves, however, replacement is necessary.

Credit for developing valvular prostheses belongs to many investigators, but the ones who first brought total valvular prostheses to popular clinical use were Starr and Edwards [7], who described their silicone ball-valve prosthesis in 1961. Later, Cartwright and associates [8] described a full-orifice, caged-ball device in which the ball fit inside the valve ring. Eventually, more durable valves became available. Along with Sam Goodenough and Paul Kahn, my colleagues and I [9] designed a valve based on this principle, but we used a biconical Pyrolite disc instead of the silicone ball.

In patients who have advanced deterioration of the valve, usually as a result of severe rheumatic valvulitis, replacement should be done with a properly selected prosthesis. The choice of a mechanical valve or a bioprosthesis depends on many factors, including the age, sex, and socioeconomic status of the patient, as well as any history of bleeding, which would make anticoagulation hazardous. The improvement in mechanical prostheses, especially those of bileaflet, low-profile design fabricated with Pyrolite carbon, has encouraged us to use them in the majority of patients [10]. In patients in whom mechanical prostheses are contraindicated, however, porcine bioprostheses can be used, although their durability is usually limited (8 to 10 years) [11]. Our experience with xenograft bovine pericardial valves indicated that durability was even less than that of porcine valves.

In recent years the approach to valve replacement for mitral stenosis has changed. Evidence is now clear that the chordal attachments to the papillary muscles should be preserved to enhance ventricular function postoperatively [12]. Thus, in most cases, only the anterior leaflet is removed, which preserves the posterior leaflet and chordal attachments. Preservation of the posterior leaflet also avoids the dreaded complication of posterior rupture of the annulus after valve replacement.

Mitral regurgitation presents a more diverse pathology and may be due to leaflet abnormality, annular dilatation, or a combination of these elements. Mitral valve prolapse is a common cause of regurgitation that lends itself readily to repair unless the annulus is calcified. If a partial rupture of the posterior leaflet has occurred, the flail scallop is excised, the remaining leaflet is repaired, and the annulus is reduced and supported by a circumferential fabric ring. Mitral regurgitation frequently accompanies ischemic myocardial disease and generally responds to annular repair alone, as the leaflets are usually normal. Valvuloplasty does not require postoperative anticoagulation.

In a small series of patients with regurgitation due to prolapse, we have used intravalvular or in situ implantation of a low-profile valve prosthesis [13]. This technique maintains the integrity of the left ventricular attachments and the function of the chordae tendineae and papillary muscles, which may decrease the incidence of postoperative left ventricular dysfunction that has been noted after standard mitral valve replacement [12]. The results in general have been favorable.

Suture technique for implantation of mitral prostheses is at the option of the surgeon. In most of our patients mattress sutures with felt pledgets are used, placing the pledget in a supraannular position. In some patients with a favorable annulus a continuous suture of 2-0 polypropylene is used. No difference has been noted in the incidence of dehiscence. When perivalvular leak occurs,

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hemolysis usually follows and may require reoperation for repair. Although most complications of this type result from infection, in some instances they occur when the annular tissue is of marginal quality for suturing.

From 1977 through June 1988 at the Texas Heart Institute we performed mitral valve replacement in 1,899 patients (54.4%) and mitral valve repair in 1,592 patients (45.6%). Of the patients who underwent mitral valve replacement, 48.7% were men and 51.3% were women. Of the patients who underwent mitral valve repair, 45.2% were men and 54.8% were women. Although the number of valve replacements for mitral valve disease has decreased in the past few years, the number of repairs has increased proportionally. This trend reflects the increasing number of patients being referred to interventional cardiologists for valvuloplasty and the current thought that, when possible, repair of the mitral valve should be attempted before replacement is considered.

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Tricuspid Regurgitation Associated With Mitral Valve Disease: Repair and Replacement

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Between January 1975 and June 1988, 156 patients with combined mitral and tricuspid valve disease underwent mitral and tricuspid valve repair or replacement. There were 127 (81%) patients with tricuspid valve repair and 29 (19%) patients with tricuspid valve replacement. Hospital mortality was 14% and was strongly influenced by preoperative pulmonary hypertension (systolic pressure > 65 mm Hg) and poor left ventricular function (ejection fraction < 0.4). Five-year survival for the entire series was 57% ± 5%; 12-year survival was 44% ± 9%. Ejection fraction was the only age-adjusted risk factor for long-term survival. Of the patients who underwent tricuspid annuloplasty, 91% ± 4% were free from reoperation after 10 years, indistinguishable from valve replacement (90% ± 7%). Our tricuspid annuloplasty is simple and effective, and exhibits excellent long-term durability as well as immediate hemodynamic improvement.

(Ann Thorac Surg 1989;48:S93–5)

As is the case for the mitral valve, tricuspid valve repair is preferred over replacement. The technique of tricuspid annuloplasty was first reported by Zubiate and Kay in 1964 [1] as a treatment for tricuspid regurgitation associated with tricuspid stenosis. In 1965, Kay, Maselli-Campagne, and Tsuji [2] reported the first series of pure tricuspid regurgitation treated by annuloplasty. Essentially the technique has not changed since then and consists of narrowing the tricuspid annulus by doing away with the posterior leaflet and creating a competent bileaflet valve. Subsequently other annuloplasty techniques have been proposed [3–5]. There have been few reports regarding long-term durability and the debate over selecting the best technique continues. This study provides a 12-year follow-up on patients with tricuspid regurgitation associated with mitral valve disease who required repair or replacement of both valves.

Patients and Methods

Clinical Characteristics

Between January 1975 and June 1988, 1,449 patients required mitral valve operation. Eleven percent (156 patients) had tricuspid regurgitation associated with mitral valve disease and underwent tricuspid and mitral valve repair or replacement.

Patients ranged in age from 17 to 87 years (mean age, 61 ± 11 years); 108 were women (69%) and 48, men (31%). Preoperatively, 63 patients were in New York Heart Association functional class III (40%) and 93 were in class IV (60%). Mean systolic pulmonary artery pressure was 59 ± 23 mm Hg. Mean left ventricular ejection fraction was 57 ± 0.14. Ninety-seven patients had a positive history of rheumatic fever.

Despite an aggressive policy of valve repair, primary mitral valve replacement was necessary in 141 patients (90%). Four patients (3%) had previous mitral replacement, and 11 (7%) underwent repair. Concomitant aortic valve replacement was performed in 25 patients (16%) and coronary artery bypass grafting in 19 patients (12%). Tricuspid repair was done in 127 patients (81%). Twenty-nine patients (19%) had severe organic changes in the tricuspid leaflets and required tricuspid replacement. For tricuspid replacement, the Ionescu-Shiley valve was used in 11 patients, the Kay-Shiley valve in 7, the Hancock valve in 5, the St. Jude Medical valve in 3, the Carpentier-Edwards valve in 2, and the Medtronic Hall valve in 1.

Operative Technique

The details of the operative technique of tricuspid annuloplasty were described in 1965 [2] and have not changed. In short, the method consists of converting an incompetent three-leaflet valve into a competent two-leaflet valve. Two, or at most three, figure-of-8 sutures of No. 2 silk or mattress sutures with Teflon felt are placed in the annulus of the posterior leaflet. A loose two-finger-breadth opening is desired. After the procedure, cold saline solution is injected through the tricuspid valve into the right ventricle to test the competence of the valve.

Results

There were 22 hospital deaths (14%) in the entire series. Systolic pulmonary artery pressures greater than 65 mm Hg (risk ratio of 3.07, $p = 0.0041$) and left ventricular ejection fraction less than 0.40 (risk ratio of 2.7, $p = 0.0103$) were independent risk factors for in-hospital death.

There were 35 late deaths. The actuarial survival rate for the entire series (hospital deaths included) was 57% ± 5%

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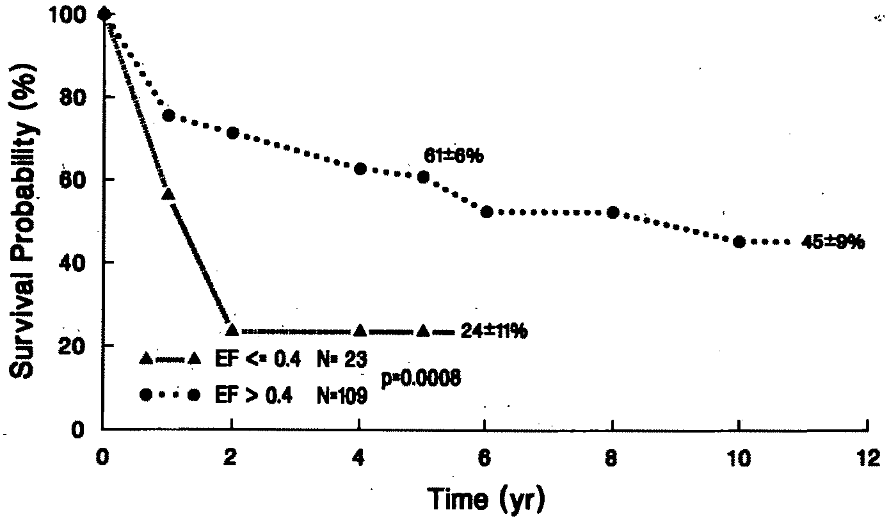
Fig 1. Comparison of survival probability between patients with normal and poor ejection fraction.



at 5 years and 44% ± 9% at 12 years. Figure 1 shows the effect of left ventricular ejection fraction on survival, which was the only significant determinant after adjusting for age. Figure 2 shows there was no statistical difference in long-term survival between patients receiving tricuspid repair and replacement (60% ± 6% versus 47% ± 10% at 5 years, respectively). However, among patients with elevated pulmonary artery pressures and poor left ventricular function, patients who underwent repair seemed to do better than those with replacement, but the numbers are too small for statistical analysis.

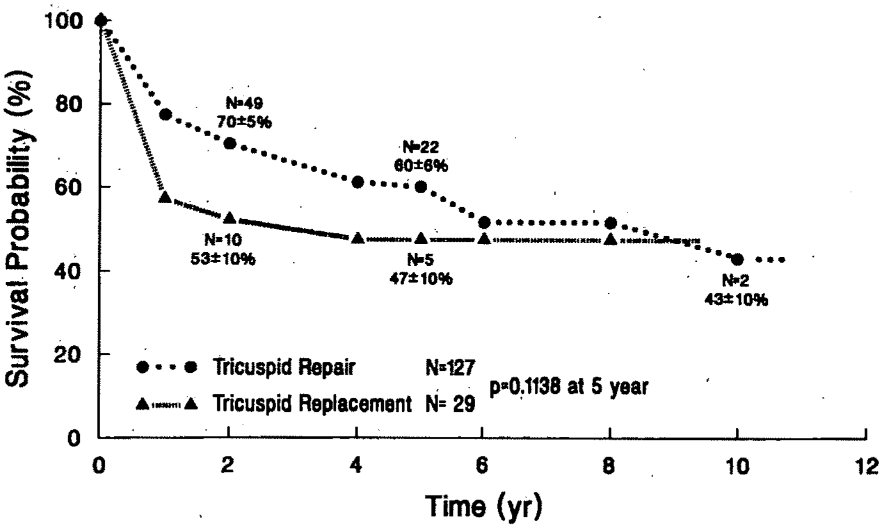
At 10 years, 91% ± 4% of the patients who had undergone tricuspid repair and 90% ± 7% of the patients who had undergone replacement were free from reoperation for tricuspid valve dysfunction (Fig 3).

Comment

This study demonstrates the excellent long-term results of this technique of tricuspid valve repair. Doing away with the posterior tricuspid leaflet is simple, quick, hemodynamically effective, and durable. It carries no risk for heart block because the posterior leaflet annulus is far from the conduction system. It is important to take a good bite of the annulus with large sutures (No. 2) to ensure durability. We abandoned use of inferior caval snares to prevent inadequate drainage and the resulting increased back pressure, which can cause lethal postoperative liver dysfunction [6]. When the right atrium is opened, several pump suctions are placed at the orifice of the inferior vena cava to obtain a bloodless field. Complete correction of the mitral valve dysfunction is mandatory. Frequently this can only be done by replacing the valve. Digitalis and fluid restriction are essential to avoid heart failure postoperatively. Based on our experience and that of Nakano and co-workers [7], this technique for tricuspid annuloplasty sets a high standard for the treatment of tricuspid regurgitation.

This study was supported in part by The Los Angeles Thoracic and Cardiovascular Foundation.

Fig 2. Comparison of survival probability between patients receiving tricuspid valve repair and replacement.



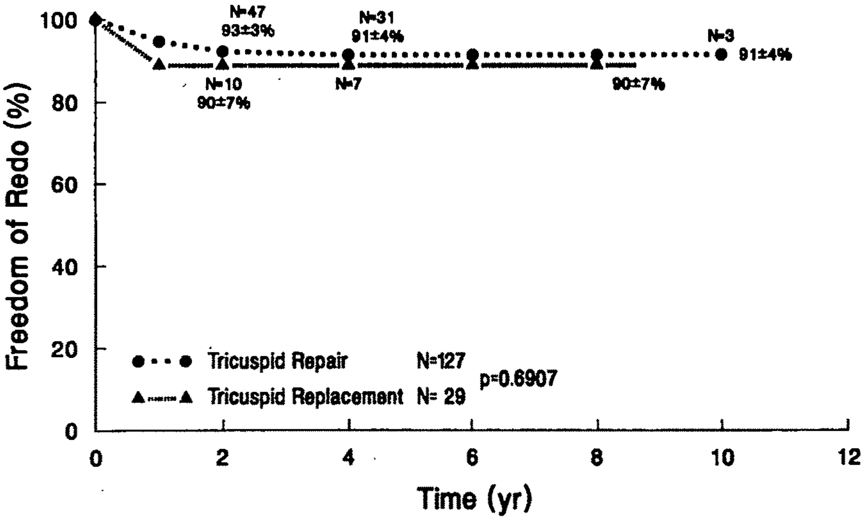


Fig 3. Valve durability of tricuspid valve repair and replacement.

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The Flexible Monocusp Valve: The Second and Third Successful Mitral Valve Replacements

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The flexible monocusp valve was developed during 1959 and 1960 while I was a Fellow in General and Cardiothoracic Surgery at the Mayo Clinic. My thesis adviser for the Master of Science in Surgery was F. H. Ellis, Jr. He suggested that as a project, I should develop a mitral valve prosthesis. The project was started with an intense multispecies study of normal mitral valve anatomy and physiology [1]. From this study, it was considered that the ideal design should have a low profile (to avoid septal contact and outflow obstruction), central flow, and occluding mechanisms that moved as far as possible across the flow path during opening and closing rather than up and down in the direction of flow. To do this the occluder needed flexibility. However, we decided for practical reasons to achieve this without using chordae [2].

Ellis conceived the idea of an open cell sponge to allow permanent fibrous union with the recipient. Doughnuts of "Ivalon" sponge, placed under inflow stasis on the atrial side of the tricuspid valve, acquired a smooth, shiny cellular covering and firm fibrous healing after 2–3 months. It seemed that the problem of developing an artificial mitral valve would be solved by the addition of a valve mechanism to an Ivalon ring.

This was done, and the first valve was used to replace the mitral valve of a mongrel dog. The animal survived the operation. Three days later, he developed sudden paralysis of the hind legs and was immediately killed. An embolus was found occluding the trifurcation of the abdominal aorta. There were also fresh renal infarcts. The emboli had come from the area of the valve. Thrombus was attached at the junction of mitral tissue and artificial material, and more particularly at the site of tissue injury produced by the sutures. This had grown over the sewing ring to the central orifice of the valve. From there some had propagated out into the bloodstream and some had broken away and embolized. The material used for this first device was silicone rubber, to which clots did not adhere, so that thrombi extending into the orifice from the ring were bound either to form an obstruction, if they remained attached to their source, or to embolize if they did not. The problem of thrombosis and embolism encountered in this first experiment thereafter dominated the development of a mitral valve prosthesis. The original thesis was confirmed in many experiments. The influence of flow was clearly demonstrated. Areas of stagnant flow were demonstrated in flow visualization studies using the pulse duplicator; at these sites the thrombus grew larger.

Many variations of design and material were tried. The ring shape and occluder mechanism were varied to prevent stasis. Insufficiency was introduced at areas of presumed stasis. Negative charges were induced on the surface to repel the platelets and cells. Valves were inserted with running 3-0 silk sutures within the annulus or on the ventricular side so that a retained rim of normal cusp tissue covered the prosthetic ring and minimized the exposure of injured tissue [3, 4].

From all of this the flexible monocusp valve emerged as the ideal design. It had a D-shaped ring: the straight portion was aligned with the base of the excised anterior cusp. The artificial cusp was attached to the straight side of the ring and had hinges parallel to this. Between the hinges, the rigid portions of the cusp met the ventricular surface of the ring in closing. The cusp thus "rolled" to and fro across the flow path in opening and closing. The valve was made of layers of laminated mylar and joined by Schjelbond glue. Based on increasing success with the animal work, leading to a 72-day survival in 1 dog, it was decided to proceed with human implantation.

For the human cases the valve was covered entirely with knitted Dacron cloth. This was done with the expectation that the inevitable fibrin deposit would adhere and ultimately be replaced by the thin neointima that regularly covered the Ivalon sewing ring. Durability and freedom from thromboembolism was the hoped-for gain. This was then the first low-profile, fabric-covered valve. It had central flow and was, with its flexible cusp, a hybrid polymer/mechanical device. Its design precluded outflow tract obstruction. Gradients varied between 0 and 7 mm Hg, and there was a minimal puff of insufficiency in closing. On ausculation it could not be distinguished from a normal natural valve.

The first two valves were made on the kitchen table of a Quonset hut in Rochester, Minnesota, and inserted on July 16 and July 22, 1960. Both patients were in functional class IV; one had a failed annuloplasty. Both survived operation and were discharged from the hospital greatly improved. They were the second and third hospital survivors of mitral valve replacement and, at that time, the only living patients in the world with artificial mitral valves.

One month later on a Friday evening we heard that the first patient had died of pulmonary edema while watching the weekly school football game. We rented a Beechcraft and flew to Marshalltown, Iowa, where we performed the autopsy in a local undertaker's parlor watched by many local citizens. The 3-0 silk suture had broken and the valve

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had undergone dehiscence. The valve itself was intact and covered with a thin layer of fibrin.

A meeting, "Artificial Valves for Cardiac Surgery," was scheduled for September 9 and 10 at the Palmer House in Chicago. We went to the meeting thinking we had the only live patient with an artificial mitral valve. We arrived to be met by Charles Hufnagel, who had just performed an autopsy on our patient in Washington, DC. He too had suffered from breaking of the 3-0 silk suture and dehiscence of the valve, which once again showed no more than a thin fibrinous coating with no identifiable thrombi. Without anticoagulation, these two patients had had no emboli, but invasion of the sewing ring by fibrous tissue had not occurred from the scarred rheumatic annulus, and 3-0 silk sutures (satisfactory for the normal dog) had simply not been strong enough in the larger human annulus.

The valve was never commercially developed but its use did continue [5]. The inventor returned to his home overseas. Instead of being made on a kitchen table, the valve was manufactured by an engineer at a local electronics plant. Interrupted 2-0 silk sutures were used for its insertion. During 1962 and 1963, 14 valves were inserted with one death from air embolism. By then, the Edwards ball valve was already being marketed and 67 of these were inserted with 12 deaths. During an average of 18 months follow-up, the ball valves had nine emboli (2 fatal), while the monocusps had one, and at autopsy this came from the atrium. The valve itself was clean [6, 7].

Despite these promising results, the valve died a natural death for lack of promotion and industrial sponsorship. It was the first low-profile, central flow, flexible cusped valve and had the potential for becoming completely covered by living, self-replicating host tissue. At another time, and under different circumstances, it might have flourished.

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The Return of Elastomer Valves

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This paper concerns the heart valves to be used mainly in artificial hearts. Most of our tricusp semilunar valves are made of polyurethane. These valves have functioned in artificial hearts for up to 62 days, and have been implanted in sheep for 1 year without evidence of thromboembolism. Our valves have a wide opening, using redundant leaflets that are "bistable." Accelerated testing by air jet provides 1,000 closures per second. Regurgitation is measured in an apparatus with the help of a competent valve. All polyurethanes change with age, but Silastic does not.

(Ann Thorac Surg 1989;48:S98–9)

The Philadelphia Drive System has a gentle dp/dt [1]. The vortex flow in the sinus of Valsalva may not be important for the closure of the valve (Henderson and Johnson, 1912), but helps prevent thrombosis.

With regard to artificial heart valves [2], we first pursued the making of monocusp valves, and these valves (made by Graham Blackbeard) functioned well; however, when tested at high speed, the leaflet descended and rubbed against the opposite wall, where a hole was ground into the leaflet corresponding with the touching area. Nature designed three leaflets and they descend together without rubbing.

Chordae tendineae serve the same purpose. A tubular valve with chordae tendineae worked well [3]. An actively operated valve would have an advantage in the mitral position.*

The material that we currently use for our polyurethane tricusp semilunar valves is Pellethane (Dow Chemical) 2363-80AE or 2363-75A, which is more flexible.† It can be used for vacuum-forming and for solution-casting. Because all polyurethanes change with age, we also use Silastic HP-100 (Dow Corning), which is claimed to be 100 times stronger than the older silicones (Fig 1).

Manufacturing

Long Sheng Yu in our lab found a simple way to make polyurethane valves with a wide opening and redundant valve leaflets. These valves are bistable, meaning that they have a tendency to be either open or closed. For the Silastic valves we use a cylindrical mold, and the stents are molded at the same time. Flexible Silastic stents offer redundancy when the valve closes.

Functional testing is done with the valves placed in artificial hearts in the cascade mock circulation. Plotting venous or filling pressure against cardiac output results in a Starling curve [4], presenting the function of the valve in the conditions in which it is going to be used (Fig 2).

The volume of regurgitation per minute is measured in a simple apparatus with the valve to be tested in the mitral position and with a nonregurgitant valve in front of it [1].

Durability testing is performed in real time with the valves mounted in artificial ventricles and connected to

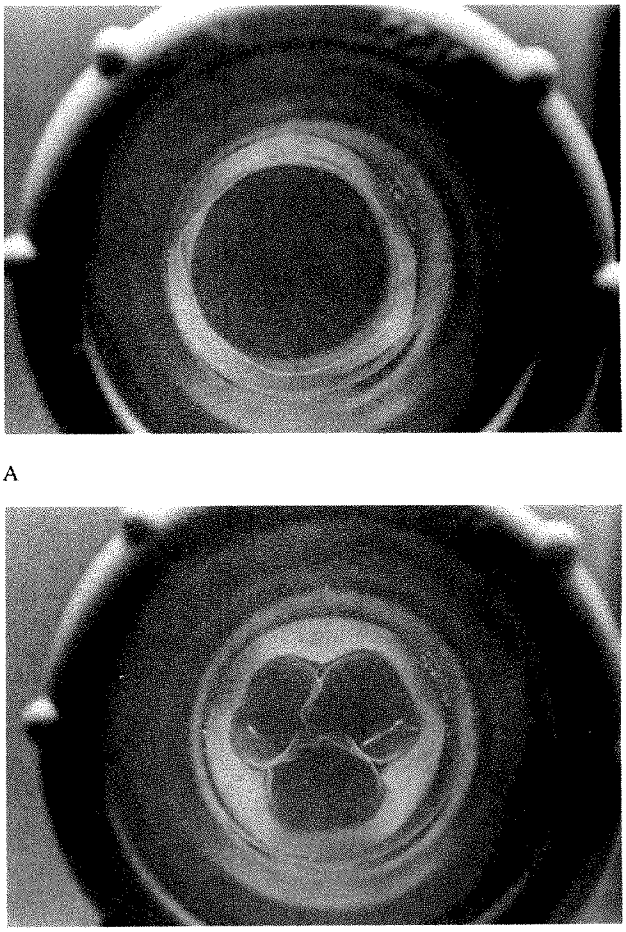

Fig 1. Silastic valves made by Holger Werning in our laboratory at the University of Utah: (A) wide open; (B) closed. Flexible stents cause redundancy of the leaflets.

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* The mushroom type of valve is described in US Patent No. 3,641,591.

† The technique of making vacuum-formed valves without seams is described in Patent Nos. 4,473,423 and 4,510,628.

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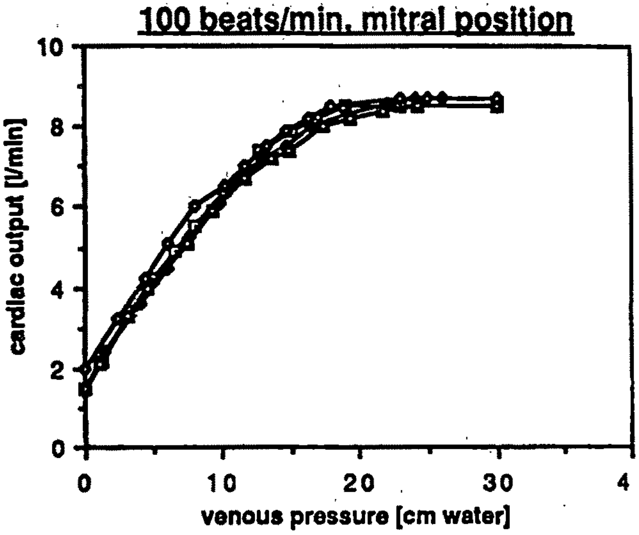

Fig 2. A Starling curve made with an artificial heart using different types of valves. The curves are almost identical. (⊡ = Silastic; ◆ = Björk-Shiley; □ = Medtronic Hall; ● = St. Jude.)

mock circulations or in various accelerated test devices. Highly accelerated testing in an air jet tester flexes the valve 1,000 times per second (the experience of a year in 9 hours) [1]. Accelerated tests break the valves at the same locations as do real-time tests.

Testing for thrombosis is done in the blood-bag system, which provokes thrombosis, and in the PAPAS (pulmonary artery to pulmonary artery shunt), which makes ex vivo testing possible for many artificial hearts in one animal.

Results of Animal Testing

Our polyurethane valves have been implanted by Dr Donato Sisto (Albert Einstein College of Medicine, New York) in 5 juvenile sheep, and they have done well. Calcification caused the death of the first sheep after 15 months. There was no breakage and no thromboemboli.

Artificial hearts of the Philadelphia type have no quick connects (to avoid thromboemboli). The atria, aorta, and pulmonary arteries are directly connected to the ventricles [5].

In the Philadelphia type I artificial heart, valves can be sewn in. In the Philadelphia type II heart, the valves are inserted beforehand in the ventricles and have been provided with a sinus of Valsalva. In both types, our polyurethane valves have been nearly free of thrombosis [1, 5].

The Future

In 1987, 46 total artificial hearts driven by compressed air were used as a bridge to heart transplantation, and 36 of these recipients have left the hospital with a functioning transplant [6]. It makes no sense to use four valves costing from $2,000 to $4,000 each when an artificial heart, in many cases, is used for only a few days. Polyurethane valves are inexpensive and sufficiently reliable and our artificial hearts are sufficiently free of thrombosis to justify their use as a bridge to donor heart transplantation [7].

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Vital Fluorescent Staining of Human Endothelial Cells, Fibroblasts, and Monocytes: Assessment of Surface Morphology

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Vital fluorescent staining of human endothelial cells, fibroblasts, and monocytes seeded on a variety of surfaces has been carried out to develop a method for studying cell growth and interactions on viable cells. Using special fluorochrome markers and monoclonal antibodies, it was possible to differentiate different cell types as they grew on polymer surfaces similar to ones that are presently used on artificial heart valves and vascular grafts.

(Ann Thorac Surg 1989;48:S100–2)

In studies carried out at the National Heart Institute in the 1960s, growth of nonthrombogenic autologous tissue layers was observed on the fabric lattices used to cover the support frames of homograft valves and rigid prostheses with moving poppets [1, 2]. Moreover, flexible polyurethane leaflets of varying porosities that were nonthrombogenic when implanted in the valve annulus of host animals could be made [3]. This work was extended to patients by covering ball valve prostheses with a similar fabric before implantation. Over the following decade, these fabric lattices were studied histologically after retrieval of the valves from patients coming to reoperation or autopsy [4, 5]. These studies confirmed that use of a favorable lattice, in the absence of undue abrasion by a moving poppet, encourages growth of a living tissue layer which shows minimal calcification, even after a decade.

Recently, we have begun a series of experiments to examine the relationship between cell matrix materials and artificial surfaces, using vital fluorescent staining [6]. We hypothesized that the requirements for optimal cell growth were best studied in vitro in living cells actively growing on a polymer surface. Toward that end, the behavior of endothelial cells, blood monocytes, and fibroblasts seeded on synthetic surfaces was monitored by fluorescence microscopy after cellular uptake of selected fluorescent markers.

Material and Methods

Human umbilical vein endothelial cells were harvested with collagenase and subcultured in medium 199 (M.A. Bioproducts) with 20% fetal calf serum (Gibco), 50 μg/mL ECGS (Biomedical Technologies, Inc) and 100 μg/mL heparin. Human monocytes were obtained from heparinized whole blood using a Ficoll gradient, and cultured in RPMI-1640 medium (Whittaker). Human fetal fibroblasts (MRC-5) were obtained commercially, and cultured in Dulbecco's minimal essential medium. After 24 to 72 hours in culture, nonadherent cells were removed by gentle rinsing before the addition of solutions containing fluorescent probes in 0.5 mL of medium. Cells were grown on 12-mm coverslips coated with either 1% gelatin, 0.5% Biomer (a segmented polyether polyurethane; Ethicon, Inc) plus human fibronectin, or Cell-Tak (an adhesive protein derived from the mussel *Myelitis edulis;* Biopolymers, Inc).

Endothelial cells were labeled with fluorescein isothiocyanate (FITC)-labeled or rhodamine-labeled *Ulex europaeus I* lectin (Vector Laboratories) after a one-hour incubation (50 μL). Monocytes were labeled with MO2-FITC (one hour incubation; 50 μL) or MO2-biotin (0.5 hour; 50 μL) followed by avidin-phycoerythrin (0.5 hour; 25 μL; Phycoprobes; Biomedia Corp). Fibroblasts were labeled with rhodamine 123 (one-hour incubation, 50 μL; Molecular Probes) or rhodamine-labeled phalloidin (two-hour or 24-hour incubation, 50 μL; Molecular Probes). Uptake of fluorescein diacetate over one minute (stock solution of 5 mg/mL in dimethyl-sulfoxide, diluted 1:1,000) was used to monitor viability of endothelial cells and fibroblasts previously labeled with the above fluorochromes; viability of monocytes was monitored by exclusion of 0.4% trypan blue. All fluorochromes were incubated with living cells; control experiments demonstrated fluorescent staining patterns similar to those seen in fixed cells.

Results

Human umbilical vein endothelial cells were plated at low density (8×10^4 cells per coverslip). In Figures 1A–C are shown the phase image (A) and staining of 24-hour-cultured endothelial cells with *Ulex europaeus*-rhodamine lectin (B) and FITC-diacetate (C), demonstrating charac-

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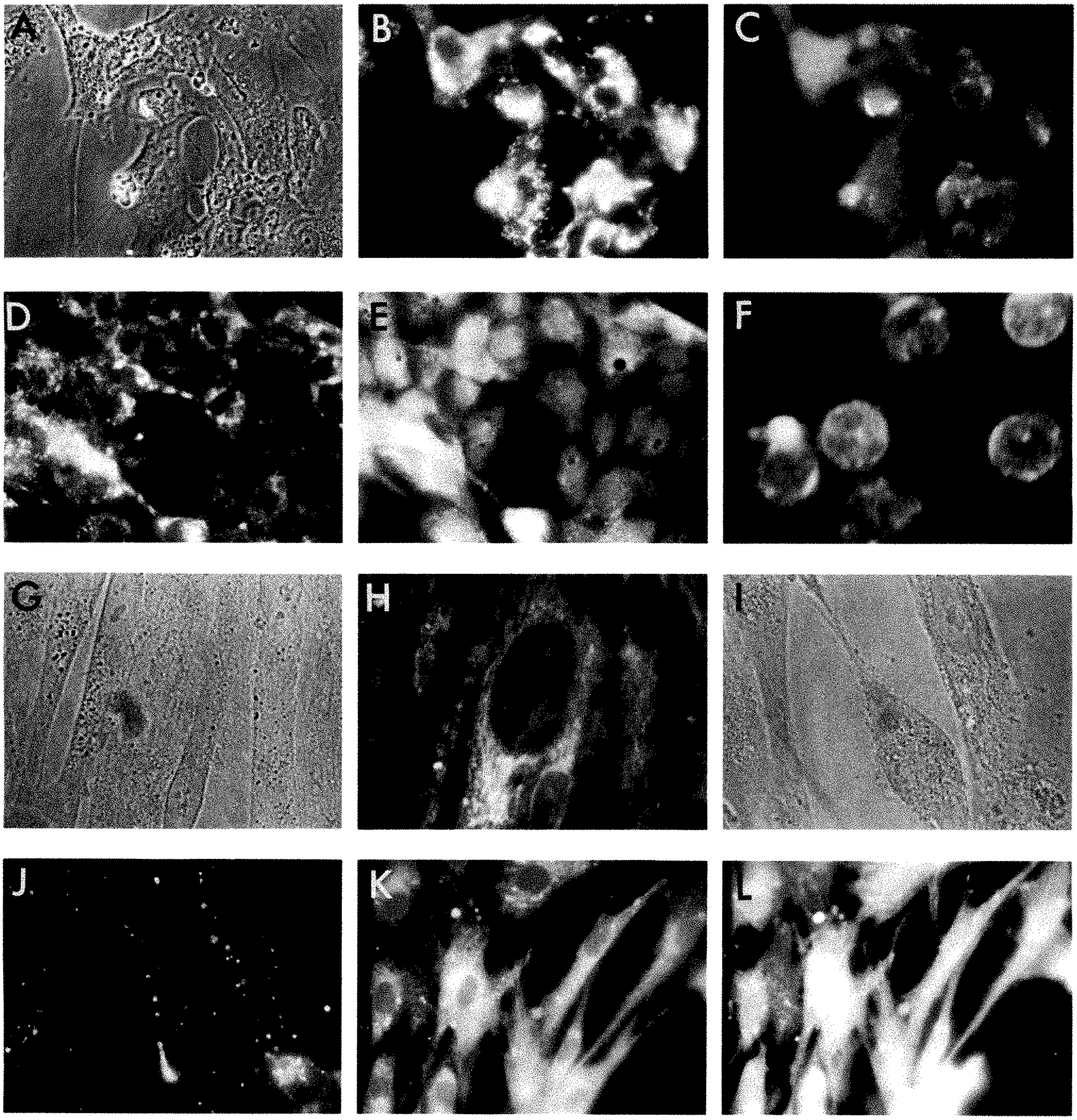

Fig 1. Vital fluorescent staining of endothelial cells, monocytes, and fibroblasts. Endothelial cells grown 24 hours on 1% gelatin are shown by phase microscopy (A; ×400), after staining one hour with Ulex europaeus*-rhodamine lectin (B; ×400), and after one minute uptake of FITC-diacetate, showing preservation of cell viability (C; ×400). After being cultured for 48 hours, cell density is greater, as shown for a different plate (D:* Ulex europaeus*-rhodamine lectin; E: FITC-diacetate; ×400). Monocytes stained with MO2-biotin-avidin are shown in (F) (×400). Fibroblasts are shown under phase microscopy (G, I) and stained one hour with rhodamine 123 (H; ×1,000) or 24 hours with rhodamine-phalloidin (J; ×1,000). Even after 24 hours of coincubation with rhodamine 123 (K), fibroblasts retain viability and their characteristic morphology (L; FITC-diacetate; ×400). (All magnifications are before 37% reduction.)*

teristic morphology with excellent viability. Confluence was achieved after 48 to 72 hours in culture: Figures 1D–E demonstrate the increased cellular density with retention of rhodamine-lectin staining and viability at 48 hours. Cell morphology and fluorochrome uptake were consistent and similar whether the cells were grown on 1% gelatin (Figs 1A–E), Cell-Tak, or Biomer with fibronectin. Fibroblasts and monocytes were not stained by *Ulex europaeus*-fluorochrome.

Monocytes stained uniformly with MO2-biotin/avidin/phycoerythrin (Fig 1F) and MO2-FITC while retaining viability, as documented by uptake of FITC-diacetate. Endothelial cells and fibroblasts did not stain with the MO2-conjugated probes.

Optimal staining of MRC-5 fibroblasts with rhodamine 123 was achieved after one hour; overnight incubation of fibroblasts was optimal for staining with rhodamine-phalloidin. Fibroblasts were consistently labeled with these probes, but exhibited contrasting patterns of fluorescence. Rhodamine-phalloidin produced a limited pattern of punctate intracellular fluorescence (Fig 1G, phase; Fig 1H, fluorescence). In contrast, bright intracellular structures were visualized with rhodamine 123 (Fig 1I, phase; Fig 1J, fluorescence). In both cases, cells retained viability, even after overnight incubation (Fig 1K, overnight rhodamine 123; Fig 1L, overnight rhodamine 123 followed by one-minute incubation with FITC-diacetate).

Comment

In these studies we have demonstrated that a specific group of fluorescent markers can be applied to living cells, with no evidence of toxicity over many hours in culture. Endothelial cells, monocytes, and fibroblasts have been examined while growing on a variety of biomatrix materials, using fluorochromes that enable identification of cellular types and their easy visualization by fluorescence microscopy. The lectin from *Ulex europaeus* has previously been shown to bind to surface glycoproteins and juxtanuclear structures representing the Golgi apparatus in endothelial cells [7], whereas the monoclonal antibody MO2 binds to surface antigens on monocytes [8]. Although rhodamine 123 and rhodamine-phalloidin (which bind to intracellular mitochondria and F-actin, respectively) [9, 10] do not specifically label fibroblasts, they have proved to be particularly useful in visualizing growth of these cells on a biomatrix.

The experimental approach presented here will enable detailed studies of the cells that normally line cardiovascular channels and their interaction with biomatrix materials. We can thus examine the requirements for, and modulation of, tissue layer growth on the biosynthetic components of artificial heart valves and cardiac assist devices, as well as the effects of biomatrix composition on cellular morphology. Moreover, this in vitro approach will allow exploration of the effects of clinical treatment modalities on tissue growth (eg, focal destruction of the vascular lining by laser treatment). The knowledge gained may be critically important for the future design of cardiovascular prosthetic devices and our understanding of the tissue response to these materials.

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Heart Valve Legislation and Regulation

Larry R. Pilot, Esq

When Art Beall telephoned me a few months ago to ask if I would be interested in addressing the World Congress on Heart Valve Replacement, I accepted without hesitation. This was because years ago Art and other speakers in this program, in particular Dwight Harken, were visible in their considerable efforts to stimulate involvement of the cardiovascular medical community to influence and direct the Food and Drug Administration (FDA) and Congress on changes to the Federal Food, Drug, and Cosmetic Act.

Their interest began in earnest with a 1969 conference sponsored by the Association for the Advancement of Medical Instrumentation and the National Institutes of Health and continued through enactment of the Medical Device Amendments of 1976. During that 7-year period, cardiovascular surgeons were probably the most influential group of health care practitioners involved in the legislative process. The 1976 Amendments were a direct product of the 1969 Association for the Advancement of Medical Instrumentation conference and a Health, Education and Welfare Departmental Task Force chaired by Theodore Cooper, who was then Director of the Heart and Lung Institute. This marvelous and carefully developed legislation was intended to produce a beneficial regulatory process that would protect the public, encourage efficient development of safe and effective devices, and avoid the harsh criticisms directed at the FDA for its delays in approving new drugs.

A major feature of the 1976 Amendments was the provision for scientific review by a peer review committee of qualified experts who were not employees of the FDA. It was believed that the premarket approval of devices could be simplified and facilitated by having experts review data on safety and effectiveness and provide their opinion to the FDA. This system would relieve FDA employees of the pressures associated with making decisions about matters in which they did not have expertise or that required application of unique expertise. The advisory panel would consist of qualified experts with expertise in clinical and administrative medicine, engineering, biological and physical sciences, and other related professions, as well as a nonvoting representative of consumer and industry interests. It was expected that this public process would produce the best possible system for scientific review and approval of new devices. That was the dream in 1976, but the reality of our experience in 1989 suggests something different.

This program is a "World Congress," and it would be nice if I could review regulatory programs throughout the world, but I will cover only the experience of the regulatory system that applies in the United States. I believe this is fair because no other country has a device premarket approval process that is as pervasive and long-standing as that administered by the FDA. I ask whether the US public, profession, and industry is better off because of the FDA's current administration of the 1976 Amendments and ask you to decide. I also make some suggestions based on my beliefs and recommendations based on my experiences.

First, I describe the current system as it applies to new devices. I then review the interests of Congress and the prospects for changes through legislation.

Regulation

The 1976 Amendments to the Act followed the major suggestions of the Cooper Committee; namely, to review and classify all known devices and require premarket approval only for devices that (1) purport or are represented to be for a use in supporting or sustaining human life or for a use that is of substantial importance in preventing impairment of human health, or (2) present a potential unreasonable risk of illness or injury. These class III devices would require the sponsor to provide adequate data in a premarket approval (PMA) application to the FDA to demonstrate the safety and the effectiveness of the device.

The FDA, with the advice of an advisory panel of qualified experts, began a review of cardiovascular devices before 1976; this process was completed after notice and comment rulemaking in 1980. As a result, the classification of all known devices can be found in Title 21 of the Code of Federal Regulations. The sponsor can determine whether a device is in class III requiring a PMA, in class II, for which compliance with a performance standard may be required, or in class I, for which the device must comply with general provisions of the Act relating to adulteration and misbranding. Any new device that has not been classified falls into class III by operation of the Act and requires either an approved PMA application or formal reclassification into class II or class I. All heart valve replacements are in class III and, by law, the FDA could ask for PMA applications for currently marketed valves that were first marketed before 1976 or were determined by the FDA to be substantially equivalent to those pre-1976 valves. On February 12, 1986, the FDA published a proposed rule in the Federal Register calling for those PMA applications and on May 13, 1987, published a final rule indicating that these PMA applications or a complicated Product Development Protocol were due on December 9, 1987.

Irrespective of whether a cardiac valve was marketed or developed before or after the 1976 enactment date of the Amendments, the same review procedure would apply. If it is necessary to investigate clinically the safety and

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effectiveness of a valve, permission for an Investigational Device Exemption must be obtained first from the FDA. Regulations appearing in 21 C.F.R. Part 812 describe the content of the application and procedure, which is intended to assure patient informed consent and Institutional Review Board approval of the protocol, among other things. The sponsor of the approved Investigational Device Exemption must comply with the regulation to assure compliance with the protocol, maintain necessary records, and submit required reports to the FDA and the Institutional Review Board, including a progress report at least annually. The FDA maintains control over the Investigational Device Exemption and can proceed to terminate an investigation for cause.

When a sponsor believes that adequate data to support the safety and effectiveness of a device have been acquired, the sponsor can provide the information required under the Act and the FDA is required to file the PMA application for review and either approval or disapproval within 180 days of the filing date. The FDA must transmit the PMA application to the Circulatory Systems Panel, which reviews the application during a public meeting and concludes by recommending either approval or disapproval of the PMA application. The FDA can either accept or reject the advice of the Panel, but it must notify the sponsor of its approval or disapproval with explanations before the expiration of 180 days from the date of filing.

That is the system—pure and simple. In theory, it makes a lot of sense. In practice, it has become worse than a nightmare on Elm Street for some developers and manufacturers. For example, some manufacturers of pre-1976 valves elected to discontinue US marketing because FDA expectations were unrealistic or excessive. Other manufacturers have been struggling to satisfy the FDA that valves that have been in the marketplace for decades are safe and effective to the extent that surgeons can decide for themselves whether a particular valve is acceptable to them for use in their patients. This somewhat controversial situation developed because the FDA staff, none of whom are surgeons, developed a draft guideline with assistance from the Advisory Panel. Among other things, this draft requests catheterization data on patients even though the patients are not symptomatic. Naturally, few (if any) surgeons would undertake to expose an asymptomatic patient to the traumatic risk of catheterization to satisfy the scientific curiosity of the FDA staff or the pleadings of the sponsor manufacturer who needs it because the FDA wants it. A similar request is in a draft guideline for new heart valves. Does it make sense to experiment with a patient who is doing well to gather data to satisfy a bureaucratic curiosity? Would any of you, after successfully surviving a heart valve replacement operation, volunteer to expose yourself to even a minimal risk of unnecessary trauma to satisfy criteria in a draft guideline prepared by the FDA? Are these data necessary? If the answers to these questions are negative, I submit that something has gone wrong with the vision we had in 1976, and there is one simple explanation. Once the 1976 Amendments became law, the medical and scientific community simply walked away and assumed that their work was finished.

If this opinion sounds harsh, ask yourselves as practitioners and pioneers in this field what you know about the activities of the Circulatory Systems Panel. How many of you know and communicate with panel members about what they are doing and whether their views reflect consensus in the cardiovascular community? What contact do your professional associations have with the Advisory Panel or the FDA, and are these associations reporting back to you on the activities of the Panel and the FDA? If you can't answer these questions or are not satisfied with your answers, clearly this wonderful and carefully designed regulatory system is not working as it was designed. The dynamic interest that produced the 1976 Amendments has become static—bureaucratic, but this does not mean that a major overhaul, or any overhaul, of the Act is necessary.

Legislation

During the last session of the 100th Congress, major efforts were made to amend the Act in areas relating to regulation of devices. The House passed a bill that almost gained Senate approval in the final days of Congress. Many legislators were disappointed, and Congressman John Dingell, Chairman of the House Committee on Energy and Commerce, is reported to be determined to accomplish his goal of legislation in the 101st Congress.

I believe there is a good possibility that the Act will be amended, although I don't believe this is necessary. Frankly, I'm surprised that Congress has not determined more thoroughly whether the FDA's application of the scientific review process has been acceptable or unacceptable. Although the House has conducted some hearings relating to the premarket notification process for devices, the Senate has not had a single hearing on the device Amendments since before 1976. If the 1976 Amendments are broken, I believe it would be helpful to identify all the broken parts before they are fixed. This would, of necessity, require investigation and hearings in which representatives of industry, the health profession, and consumers would express their views about the system.

Although I believe that the FDA in general has done a good job and that no change in the Act is indicated, I have witnessed distressing performances by the FDA. I hope these represent exceptional situations, but I have experienced many situations in which device sponsors and their medical and scientific experts leave FDA meetings with a very poor image of the FDA. For example, about a year ago, the FDA made great fanfare of a claim that there was no backlog of certain applications. To many companies, this news came as a shock, because they had PMA applications that had then been pending for at least a year. For the most part, all they wanted was the opportunity to have their PMA application reviewed in public by the Advisory Panel. I want to believe that progress has been made by the FDA, but until I see confirming evidence that is not generated by the FDA, I and others must remain skeptical. Perhaps Congress will look into these and other matters in the next session. In the meanwhile, I encourage you to examine whether this isn't a good time for you and your professional organizations to examine the dynamics of the current process so that in 25 years or less you can have another World Congress to review the beneficial changes of the future.

Current Affairs and Opportunities

Although the US at present has the most pervasive regulatory program for devices, there is concern about what governments in other countries are doing and what impact this will have on the world marketplace. At present, it appears that regulation of the device industry in other countries is generally reasonable and does not create an adverse impact on the industry. For example, in the current issue of *Medical Device & Diagnostic Industry*, Pieter Halter writes in his Market Report about interventional cardiology in Europe. He concludes that Western European countries are very much at the forefront of interventional cardiology, and he reminds the reader that percutaneous transluminal coronary angioplasty procedures originated in Europe. He reports that other procedures involving use of devices are commonplace in Europe, yet many of these procedures may not be available in the US. I believe that this may be because the regulatory process in the US has become too oppressive.

I know that US companies are commercially distributing products outside the US, but they are unable to persuade the FDA staff to file a PMA application for review by the Advisory Panel. That the FDA permits the US manufacturer to export a heart valve to other countries but refuses to submit the manufacturer's PMA application to the Panel for scientific review is both unfortunate and ridiculous. I know this to be a fact and question whether it makes sense that the FDA staff would permit commercial distribution and use of a device outside the US, but continue to refuse to present the PMA application to the Panel for a public review.

Several weeks ago, the FDA announced that it would require submission of data on the safety and effectiveness of some pre-1976 cardiovascular devices. These include vascular graft prostheses of less than 6-mm diameter and intraaortic balloon and control systems. Whether FDA expectations will be reasonable remains to be determined. I suspect that some pre-1976 heart valve manufacturers would suggest that the FDA's expectations for these preenactment devices are unreasonable, but I am not sure whether you as surgeons and developers agree. I do know that you have an opportunity to make your opinion known and to influence the practices of the FDA and its panel of advisors. Whether you elect to accept this responsibility as many of you did before 1976 is clearly your choice. If you are satisfied with the present system, then compliment the FDA and its Advisory Panel for the service they provide to the public. If you believe improvements are desirable, then either be content to let an elusive "George" do it or get back into the process and influence the direction of the FDA.

Summary

During 13 years of regulation by the FDA under the Medical Device Amendments of 1976, the process by which replacement heart valves have been developed and modified has changed. Some of these changes have been good for the public, whereas other changes are of questionable value. Conditions will never be as they were 25 years ago, but they could be closer to what was expected in 1976.

As the FDA constantly seeks to improve its performance and Congress focuses on possible changes to the Act, the cardiovascular community of practitioners, inventors, and manufacturers should offer their assistance. I believe the creative spirit that enables you as pioneers to reflect on your accomplishments and contemplate even greater innovations for the future should again be applied to the process of helping the FDA improve the way it serves us—the public.

THE ANNALS OF THORACIC SURGERY INFORMATION FOR AUTHORS

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Chapter in Book

12. Katz PO. Achalasia. In: Castell DO, Richter JE, Dalton CB, eds. Esophageal motility testing. New York: Elsevier Science Publishing Company, 1987:107.

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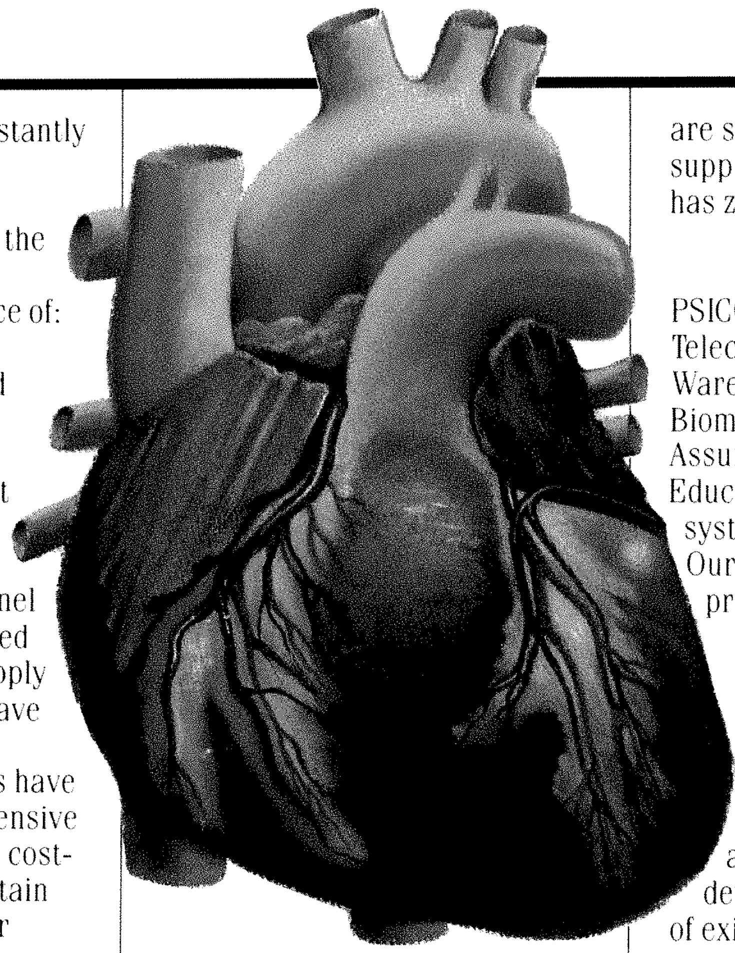

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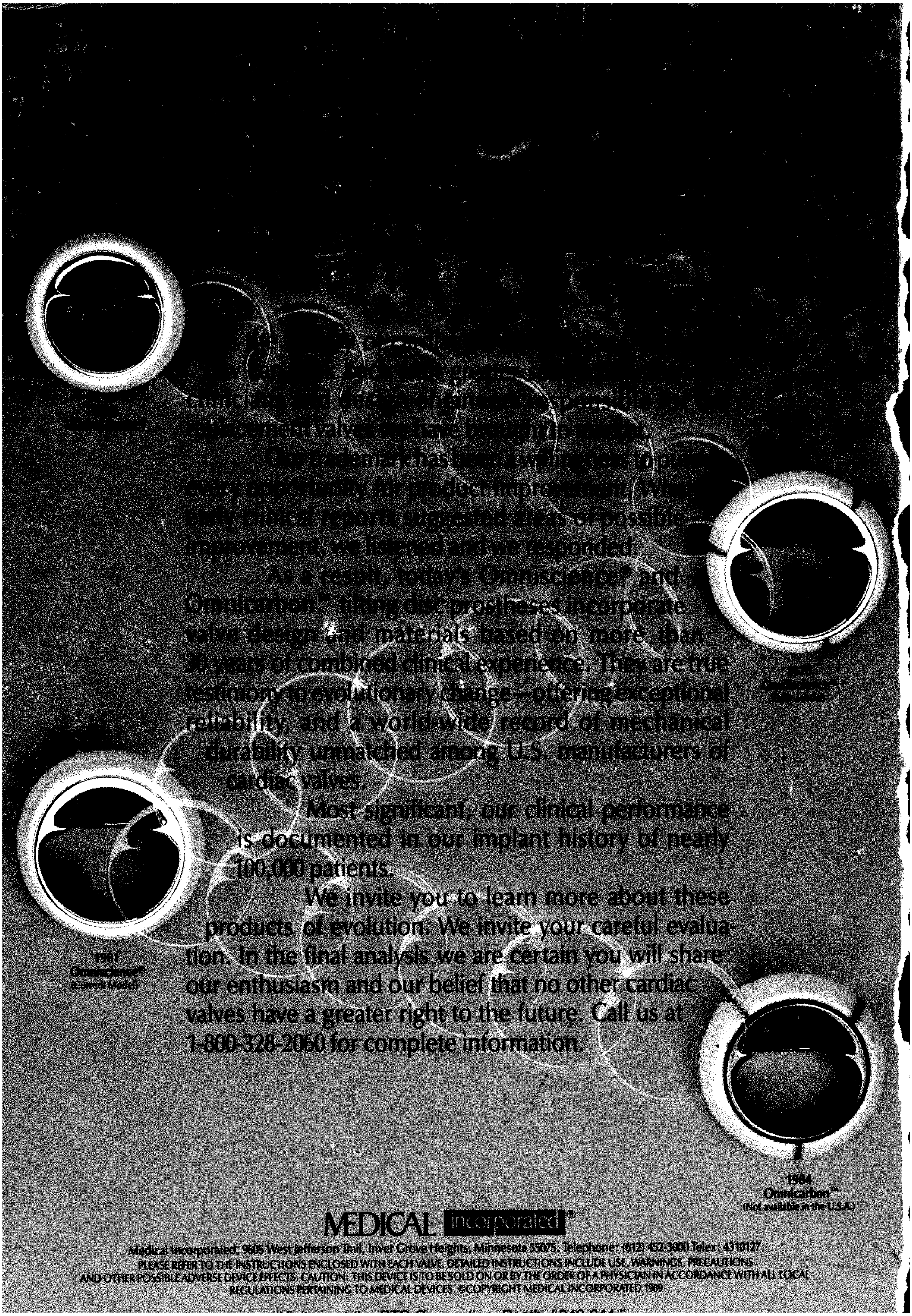

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